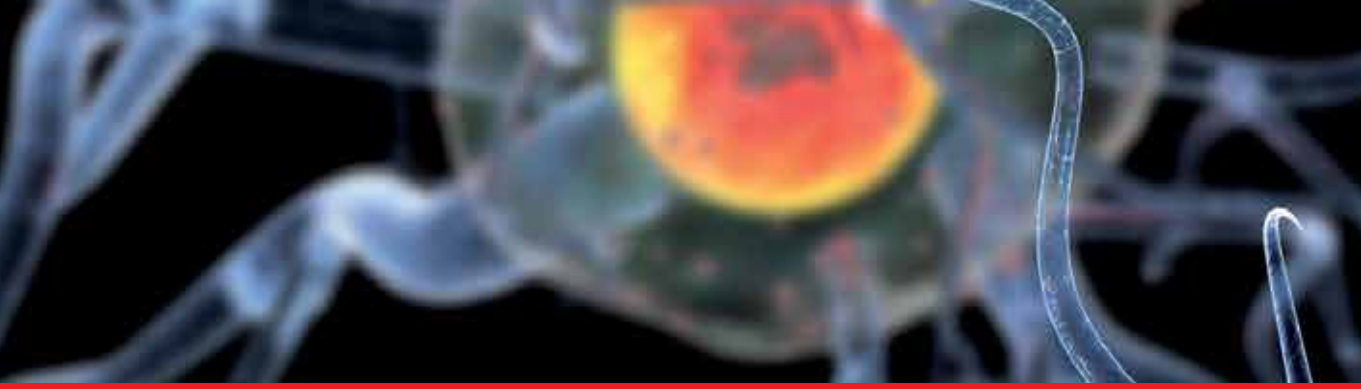
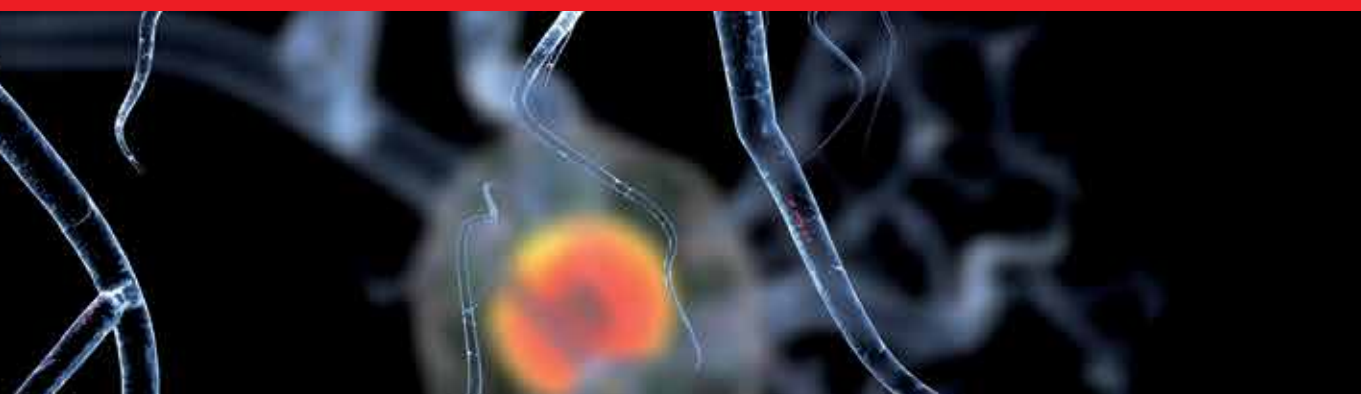


IntechOpen

Lupus

New Advances and Challenges

Edited by Sophia Lionaki



Lupus - New Advances and Challenges

Edited by Sophia Lionaki

Published in London, United Kingdom







IntechOpen






Supporting open minds since 2005

Lupus - New Advances and Challenges
http://dx.doi.org/10.5772/intechopen.73843
Edited by Sophia Lionaki

Contributors
Trine Jorgensen, Emily Zhang, Masakazu Washio, Chikako Kiyohara, Akiko Ohta, Josep Ordi - Ros, Cristina Sole Marçe, Josefina Cortes Hernandez, Gabriela Tejon, Maria Rosa Bono, Mario Rosemblatt, Yessia Hidalgo, Juanita Romero-Diaz, Maria Del Carmen Zamora-Medina, Sophia Lionaki

First published in London, United Kingdom, 2020 by IntechOpen
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, 7th floor, 10 Lower Thames Street, London, EC3R 6AF, United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Lupus - New Advances and Challenges
Edited by Sophia Lionaki
p. cm.
Print ISBN 978-1-83880-169-4
Online ISBN 978-1-83880-170-0
eBook (PDF) ISBN 978-1-83880-184-7

Meet the editor

Sophia Lionaki is a nephrologist with expertise in glomerular diseases of the kidney. She obtained her medical degree from the National and Kapodistrian University of Athens, Greece, in 1996 and her PhD in 2010 from the University of Ioannina. She did a clinical research fellowship in "Autoimmune Diseases of the Kidney" at the University of North Carolina, Chapel Hill, USA, for one year and subsequently worked for the related program of the National Institute of Health, USA, as a clinical researcher for two years. Her research interests include ANCA vasculitis, lupus nephritis, and primary glomerular diseases in the native kidneys and the renal allograft. She currently works in the Department of Nephrology of Laiko Hospital in Athens, Greece, since 2008 with clinical, research, and teaching responsibilities.

Contents

Preface

This book provides guidance on the assessment and management of patients with systemic lupus erythematosus. The book is focused on recent advances in the epidemiology, pathophysiology, pathogenesis, and management of the disease focusing on specific subgroups of patients, including the issue of infertility, a problem which is quite common among females with lupus.

The authors who collaborated in this project have summarized their experience and have presented advances in certain fields related to assessing the severity of these disorders as well as the management of such patients. The book contains six chapters, organized in three sections that cover important research aspects regarding systemic lupus erythematosus.

The first section consists of an introductory chapter prepared by the editor. This chapter presents a brief background about current concepts on the disease and future expectations regarding treatment and long-term outcomes. The next chapter deals with the incidence and prevalence of systemic lupus erythematosus and the findings from epidemiological studies on the risk/preventive factors for this chronic inflammatory disease. It presents factors that have been associated with the etiopathogenesis of lupus or have not yet been elucidated in detail, such as genetic factors and environmental factors, which are thought to play a role in its development. Related to the recent insights of pathogenesis, the next chapter describes a spontaneous mouse model of lupus with review of its histopathologic, serologic, lymphocytic, hormonal, and genetic characteristics as well as its use as a preclinical model for the testing and discovery of new drugs for human use.

The second section discusses the issue of infertility, focusing on reproductive medicine and describing diagnostic and therapeutic strategies used in the last decades that are considered important for lupus patients with infertility since they have improved the related outcomes and consequently the management of pregnancy. However, pregnancies in patients with systemic lupus erythematosus are still considered a high-risk condition due to an increased risk of major obstetrical and neonatal complications. Thus, this section presents the setting of immunologic and hormonal adaptations during pregnancy, including the presence of antiphospholipid antibodies and anti-SSA/Ro, lupus nephritis, and preeclampsia. Finally, the authors provide current knowledge regarding infertility and assisted reproduction technologies, which have emerged as a safe option in patients with systemic lupus erythematosus.

The third section describes neuropsychiatric lupus including the clinical manifestations and its treatment in lupus patients. Based on mouse studies, the authors also discuss the correlation between inflammatory mediators, such as cytokines and autoantibodies, and the development of neurological symptoms with specific emphasis on the evidence for systemic versus local effects, offering a comprehensive review of old and new studies in animal models. This provides insights into how these results align with current treatment strategies offered to patients.

The editor wishes to express his thanks to all the participants in this book for their valuable contributions and to Mrs. Nina Kalinic Babic for her assistance in finalizing the work. Acknowledgment to the IntechOpen staff members responsible for the completion of this book and other publications for free visible knowledge.

Sophia Lionaki, MD, PhD
Department of Nephrology and Transplantation,
Laiko Hospital, National & Kapodistrian University of Athens,
Faculty of Medicine,
Athens, Greece

Section 1

Introduction, Epidemiology and New Insights into the Pathogenesis of Lupus

Chapter 1

Introductory Chapter: Recent Advances in Systemic Lupus Erythematosus

Sophia Lionaki and Ioannis Boletis

1. Introduction

Systemic lupus erythematosus is the prototype of autoimmune disorder, which is typically manifesting in multiple organ systems and running a chronic course, affecting primarily females. It is associated with significant public health impact in affected individuals, with highly heterogenous presentation and progression. During the last two decades, substantial progress has been made in our knowledge on systemic lupus erythematosus incidence, pathogenesis, therapeutic interventions, and long-term outcomes. However, it remains a challenging area of research, especially considering the genetic, epigenetic, and environmental factors that have been found to play a crucial role in disease prognosis [1]. Estimates on the worldwide incidence and prevalence of lupus revealed that the highest incidence was found in North America, while the lowest rates have been reported in Northern Australia [2]. Interestingly, a registry from the island of Crete reported that the overall age-adjusted/sex-adjusted incidence is growing among males [3]. Factors such as age, gender, ethnicity, genetics, hormonal status and environmental factors appear to have a central function in the development of the disease [2].

2. The new era of systemic lupus erythematosus

Despite the significant improvements which have been achieved in the field of lupus, including the overall management and immunosuppressive agents used for therapy, mortality rates of affected patients remain three times higher than those in the general population [2]. In particular, patients with lupus nephritis, who end up in end-stage kidney disease, inquire a huge burden of morbidity, related not only to the dialysis procedure but also to the inflammatory background, the impact of cumulative immunosuppression, and the phenomenon of accelerated atherosclerosis which results in cardiovascular death [4]. Still the performance of each patient is variable. For instance, neurologic and psychiatric manifestations of systemic lupus erythematosus appear to have an increasing rate in recent reports although they are found in different frequencies across lupus cohorts, depending on the methodology used to define the related signs/symptoms and the screening practice [5]. Likewise, family planning becomes a crucial problem for women with systemic lupus erythematosus, considering the fact that females of reproductive age are the most frequently affected patients. Pregnancies in patients with active lupus and especially in those with renal involvement have been associated with significant morbidity and mortality for both the mother and the fetus [6]. Moreover, the interplay between

environmental factors and the genetic profile of each individual appear to be of great importance with respect to the onset and the progression of this disorder [7, 8]. Given these circumstances, we consider systemic lupus erythematosus a challenging field of research, which enquires continuing updating in order to illustrate all current knowledge regarding disease pathogenesis and provide guidelines for clinical practice employing all newer immunosuppressive agents.

Author details

Sophia Lionaki* and Ioannis Boletis
Department of Nephrology and Transplantation, Faculty of Medicine, Laiko Hospital, National and Kapodistrian University of Athens, Athens, Greece

*Address all correspondence to: sofia.lionaki@gmail.com

IntechOpen

References

[1] Parks CG, de Souza Espindola Santos A, Barbhaiya M, Costenbader KH. Understanding the role of environmental factors in the development of systemic lupus erythematosus. Best Practice & Research. Clinical Rheumatology. 2017;**31**(3):306-320

[2] Stojan G, Petri M. Epidemiology of systemic lupus erythematosus: An update. Current Opinion in Rheumatology. 2018;**30**(2):144-150

[3] Gergianaki I, Bortoluzzi A, Bertsias G. Update on the epidemiology, risk factors, and disease outcomes of systemic lupus erythematosus. Best Practice & Research. Clinical Rheumatology. 2018;**32**(2):188-205

[4] Mageau A, Timsit JF, Perrozziello A, Ruckly S, Dupuis C, Bouadma L, et al. The burden of chronic kidney disease in systemic lupus erythematosus: A nationwide epidemiologic study. Autoimmunity Reviews. Jul 2019;**18**(7):733-737. pii: S1568-9972(19)30114-4

[5] Tani C, Palagini L, Moraes-Fontes MF, Carli L, Mauri M, Bombardieri S, et al. Neuropsychiatric questionnaires in systemic lupus erythematosus. Clinical and Experimental Rheumatology. 2014;**32**(5 Suppl 85):S-59-S-64

[6] Nahal SK, Selmi C, Gershwin ME. Safety issues and recommendations for successful pregnancy outcome in systemic lupus erythematosus. Journal of Autoimmunity. 2018;**93**:16-23

[7] Javinani A, Ashraf-Ganjouei A, Aslani S, Jamshidi A, Mahmoudi M. Exploring the etiopathogenesis of systemic lupus erythematosus: A genetic perspective. Immunogenetics. 2019;**71**(4):283-297

[8] Patrias K. Citing Medicine: The NLM Style Guide for Authors, Editors, and Publishers [Internet]. Bethesda, MD: National Library of Medicine (US); 2007. [Updated: 2 October 2015; Cited: 13 October 2016]. Available from: http://www.nlm.nih.gov/citingmedicine

Chapter 2

Epidemiology of Systemic Lupus Erythematosus

Masakazu Washio, Chikako Kiyohara and Akiko Ohta

Abstract

Epidemiology is the study of the frequency and distribution of diseases and factors related to the development of diseases. Systemic lupus erythematosus (SLE) is a rare, chronic inflammatory autoimmune disease that affects many tissues and organs, whose female-to-male incidence ratio is 6:10 for childbearing age. Its chronic intractable nature has a significant impact on medical care utilization, activities of daily living, and quality of life. However, the etiology of SLE has not yet been elucidated in detail, although genetic factors as well as environmental factors are thought to play a role in its development. In this chapter, we introduce the incidence and the prevalence of SLE as well as factors related to the development of SLE and discuss how to prevent the development of SLE.

Keywords: SLE, epidemiology, incidence, prevalence, risk factor

1. Introduction

Systemic lupus erythematosus (SLE) is a rare, serious, chronic inflammatory autoimmune disease that affects many tissues and organs [1, 2]. The Japanese Ministry of Health and Welfare designated SLE as an intractable disease because there is no established way to cure or prevent it [3, 4]. Under a nationwide registration system for patients with intractable diseases, 55,021 SLE patients were eligible for financial aid from the Japanese government in 2007 and the prevalence of SLE was estimated to be 44 per 100,000 persons in Japan [5]. Females are 8.2 times more likely to suffer from SLE than males in Japan [5]. Serdula and Rhoads [6] reported that the age-adjusted prevalence of SLE was greater in Japanese (18.2/100,000 persons) than White People (5.8/100,000 persons) in Hawaii, but they could find no reason for the high prevalence of SLE in Japanese ancestry. The etiology of SLE has not yet been elucidated in detail, although genetic factors as well as environmental factors are thought to play a role in its development [1]. The discrepancies of rates (i.e., higher rates in certain ethnic groups) are in part due to genetic factors as well as due to environmental factors such as smoking and dietary habits [7].

In this chapter, we would like to show the incidence and prevalence of systemic lupus erythematosus (SLE) and the findings from epidemiological studies on the risk/preventive factors for SLE.

2. Diagnosis criterion of SLE (case definition)

The established diagnosis criterion of SLE is needed to estimate the frequency and distribution of the patients with SLE. However, case definition is one of the

important factors, which may influence the results of epidemiological studies. Currently, the American College of Rheumatology (ACR) 1982 revised criteria for the classification of SLE [8], as modified in 1972 (ACR-97) [9], are widely used for the diagnosis of SLE. The diagnosis of SLE requires the presence of four or more of the following 11 criteria, which are (1) malar rash, (2) discoid rash, (3) photosensitivity, (4) oral ulcer (usually painless, observed by a physician), (5) arthritis (nonerosive arthritis 2 or more peripheral joints), (6) serositis (a. pleuritis or b. pericarditis), (7) renal disorder (a. persistent proteinuria either 0.5 g/day or > 3+ if quantification not performed or b. cellular cast), (8) neurologic disorder (a. seizures or b. psychosis in the absence of offending drugs or metabolic disorders), (9) hematologic disorder (a. hemolytic anemia with reticulocytosis or b. leukopenia <4000/mm^3 or c. lymphopenia <1500 mm^3 or d. thrombocytopenia <100,000 mm^3 in the absence of offending drugs), (10) immunologic disorder (a. antibody to native DNA in abnormal titer or b. presence of antibody to Sm nuclear antibody or c. positive finding of antiphospholipid antibody), and (11) positive antinuclear antibody test result. Although the presence of four or more ACR-97 criteria is required for SLE classification, all other reasonable diagnoses of diseases other than SLE (e.g., neurologic disorder due to uremia, acidosis, or electrolyte imbalance) must be excluded [7]. Among the 11 ACR criteria, positive antinuclear antibody test result, hematologic disorder, immunologic disorder, and arthritis are the four most common criteria seen in SLE patients at the time of diagnosis [10–13] (**Table 1**).

When epidemiological studies are conducted based on the rheumatologist definition, biopsy-proven lupus nephritis patients may be considered to have SLE even though they satisfy fewer than four ACR-97 criteria. In these cases, the rates of SLE will be greater than the rates based on the ACR-97. Recently, the Systemic Lupus International Clinics (SLICC), which is an international group for the clinical research of SLE, presented a new criterion for the classification of SLE in 2012 (SLICC-12) [14]. They also validated the ACR-97 and the SLICC-12. The SLICC-12 resulted in fewer misclassification than the ACR-97 [14]. Compared with the ACR-97, the SLICC-12 had greater sensitivity but less specificity [14, 15]. The SLICC case definition of

	Voss et al. [10]	**Uramoto et al. [11]**	**Lim et al. [12]**	**Izmirly et al. [13]**
Manifestation	**Denmark**	**United States**	**United States**	**United States**
	n = 107	**n = 69**	**n = 267**	**n = 232**
1. Malar rash	52(49)	18(26.1)	55(20.6)	86(37.1)
2. Discoid rash	15(14)	14(20.3)	40(15.0)	32(13.8)
3. Photosensitivity	51(48)	26(37.7)	43(16.01)	74(31.9)
4. Oral ulcer	9(8)	4(5.8)	61(22.8)	81(34.9)
5. Arthritis	62(58)	37(53.6)	167(62.5)	159(68.5)
6. Serositis	47(44)	22(31.9)	91(34.1)	84(36.2)
7. Renal disorder	37(35)	31(44.9)	91(34.1)	81(34.9)
8. Neurologic disorder	14(13)	2(2.9)	24(9.0)	43(18.5)
9. Hematologic disorder	66(62)	55(79.7)	216(80.9)	188(81.0)
10. Immunologic disorder	99(93)	44(63.8)	187(70.0)	170(73.3)
11. Antinuclear antibody	107(100)	46(66.6)	244(90.4)	213(91.8)

Data are expressed as number (%).

Table 1.
Distribution of clinical manifestation and laboratory findings at the diagnosis of SLE.

SLE yielded higher incidence and prevalence estimates than the ACR-97 case definition [15]. Thus, the incidence and prevalence of SLE are influenced by the diagnosis criterion of SLE. Therefore, interpretation of incidence and prevalence of SLE also take into account differences in the methodology used to determine these rates.

3. Incidence and prevalence of SLE

In the United Kingdom, Rees et al. [16] found that the incidence and prevalence of SLE in White People (6.73/100,000 person-years and 134.5/100,000 persons) were smaller than those in other ethnic groups such as Black African (13.78/100,000 person-years and 179.8/100,000 persons), Black Caribbean (31.46/100,000 person-years and 517.5/100,000 persons), and Indian (9.9/100,000 person-years and 193.1/100,000 persons) (**Table 2**). In addition to the United Kingdom, American epidemiologists also reported that the incidence and prevalence of SLE in White

First author (year)	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Rees (2016) [16]	United Kingdom	1999–2012	Clinical Practice Research Datalink (CPRD)	White People	6.73	134.5
				Black African	13.78	179.8
				Black Caribbean	31.46	517.5
				Indian	9.9	193.1
Serdula (1979) [6]	United States (Hawaii)	1970–1975	American Rheumatism Association (ARA)—preliminary criteria	White People	NA	5.8
				Chinese	NA	24.1
				Filipino	NA	19.9
				Hawaiian	NA	20.4
				Japanese	NA	18.2
Lim (2014) [12]	United States (Georgia)	2002–2004	ACR-97 criteria	White People	2.7	32.7
				Black People	8.7	118.5
Somers (2014) [17]	United States (Michigan)	2002–2004	ACR-97 criteria	White People	3.7	47.5
				Black People	7.9	111.6
				Asian/Pacific Islanders	NA	24.9
Dall'Ella (2017) [18]	United States (California)	2007–2009	ACR-97 criteria	White People	2.8	NA
				Black People	15.5	NA
				Asian/Pacific Islanders	4.1	NA

NA, not available.

Table 2.
Incidence and prevalence of SLE by ethnic group in the United Kingdom/the United States.

First author (year)	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Uramoto (1999) [11]	United States (Minnesota)	1950–1979	ACR-82 criteria	Overall	1.51	NA
				Females	2.47	NA
				Males	0.50	NA
	United States (Minnesota)	1980–1992	ACR-82 criteria	Overall	5.56	NA
				Females	9.40	NA
				Males	1.54	NA
Lim (2014) [12]	United States (Georgia)	2002–2004	ACR-97 criteria	All population	5.6	73.0
				Females	9.2	127.6
				Males	1.8	14.7
				White People	2.7	32.7
				Females	4.7	59.0
				Males	0.7	7.5
				Black People	8.7	118.5
				Females	13.4	196.2
				Males	3.2	23.7
Somers (2014) [17]	United States (Michigan)	2002–2004	ACR-97 criteria	All population	5.5	72.8
				Female population	9.3	128.7
				Male population	1.5	12.8
Dall'Ella (2017) [18]	United States (California)	2007–2009	ACR-97 criteria	All population	4.6	NA
				Females	8.6	NA
				Males	0.7	NA
				White People	2.8	NA
				Females	5.3	NA
				Males	0.6	NA
				Black People	15.5	NA
				Females	30.5	NA
				Males	2.1	NA
				Asian /Pacific Americans	4.1	NA
				Females	7.2	NA
				Males	0.6	NA
Izmirly (2017) [13]	United States (New York)	2007–2009	ACR-97 criteria	Overall	4.6	62.2
				Females	7.9	107.4
				Males	1.0	12.5
	United States (New York)	2007–2009	SLICC	Overall	6.2	73.8
				Females	10.3	128.3
				Males	1.7	13.8

First author (year)	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Barnabe (2012) [19]	Canada	1994–2007	Diagnosed in clinical setting (ICD-9, ICD-10)	Females	NA	27.3
				Males	NA	3.2
				First Nations females	NA	32.2
				First Nations males	NA	3.2
				non-First Nations females	NA	27.1
				non-First Nations males	NA	3.2
Somers (2007) [20]	United Kingdom	1990–1999	Clinical Practice Research Datalink (CPRD)	All population	4.87	NA
				Females	8.01	NA
				Males	1.60	NA
Rees (2016) [16]	United Kingdom	1999–2012	Clinical Practice Research Datalink (CPRD)	All population	4.91	64.6–97.0
				Female population	8.34	NA
				Male population	1.44	NA
Arnaud (2014) [21]	France	2010	Diagnosed in clinical setting (ICD10)	All population	3.32	47.0
				Females	5.51	79.1
				Males	0.92	11.8
Zou (2014) [22]	China	2009–2010	Diagnosed by rheumatologists (ACR-97 criteria)	All population	NA	37.6
				Females	NA	70.3
				Males	NA	6.4
Yu (2013) [23]	Taiwan	2000–2008	Diagnosed in clinical setting (ICD9)	All population	8.4	37.0
				Females	15.0	66.6
				Males	1.9	8.5
Shim (2014) [24]	South Korea	2009	Diagnosed (ACR-criteria) (ICD10)	All population	2.8	24.9
				Females	5.1	42.9
				Males	0.6	7.0

First author (year)	Country	Year	Definition of SLE	Characteristics of study group	Incidence (per 100,000 person-years)	Prevalence (per 100, 000 persons)
Yamamoto (1986) [25]	Japan	1972–1983	Diagnosed by a rheumatologist (ACR criteria)	All population	2.0	NA
				Females	3.7	NA
				Males	0.25	NA
Ohno (1992) [26]	Japan	1992	Diagnosed in clinical setting (ACR-82 criteria)	All population	NA	29.1
				Females	NA	52.3
				Males	NA	5.0
Iseki (1994) [27]	Japan	1972–1991	ACR-82 criteria	All population	3.0	NA
		1972–1991		Females	1.6–4.7	6.6–68.4
		1973–1991		Males	0.4–0.8	0.8–7.0

NA, not available.

Table 3.
Incidence and prevalence of SLE in females and males in selected countries.

People were smaller than those in other ethnic groups in the United States [6, 12, 17, 18] (**Table 2**). The disease burden of SLE is highest in Black People [17, 18], followed by Asian/Pacific islanders [17] and White People in the United States [17, 18], which may be related to genetic and environmental factors.

As shown in **Table 3**, the incidence and prevalence of SLE are greater in females than in males in all studies regardless of ethnic group or countries [11–13, 16–27]. Age-adjusted incidence of SLE in females was 8.8–14.5 times greater than in males in California, the United States (i.e., 12.3-fold female excess in all population, 8.8-fold female excess in White People, 14.5-fold female excess in Black People, and 12.0-fold female excess in Asian/Pacific islanders) [18], while the age-adjusted incidence of SLE in females was 7.8–14.8 times greater than that in males in East Asia (i.e., 7.8-fold female excess in Taiwan [23], 8.5-fold female excess in South Korea [24], and 14.8-fold female excess in Japan [27]).

SLE is more common in women than men across all age groups, and this female predominance is especially noteworthy in the 15- to 64-year age group, wherein the male-to-female ratios of age-group incidence show a 6- to 10-fold female excess [28], which suggests that female sex hormones may play an important role in the development of SLE [28]. The Nurses' Health Study [29] revealed that oral contraceptive use increased the risk of SLE in the United States, whereas Bernier et al. [30] reported that it was not past use but current use of oral contraceptive pills that increased the risk of SLE in the United Kingdom. These studies [29, 30] also suggest that female sex hormones such as estrogen may play an important role in the development of SLE. In addition to sex hormones, both X-linked and autosomal immune genes are also regulated epigenetically and likely contribute to the sex difference in the incidence of SLE [31].

4. Factors related to the development of SLE

Although genetic factors are suggested to play an important role in the development of SLE, nongenetic factors are also suggested to play a role in the development of SLE [1, 7]. In addition to genetic susceptibility, hormonal and reproductive exposures (e.g., endogenous estrogens, estrogen replacement therapy), occupational and environmental exposures (e.g., silica, ultraviolet light), and infectious exposures (e.g., Epstein-Barr virus) are suggested to influence the risk of SLE [1, 7]. Complex interactions between genetic and environmental factors are thought to play a role in the development and progression of SLE [7].

4.1 Sex hormones and reproductive issues in females

The incidence of SLE is greater in females than in males in all studies regardless of ethnic group or countries [11–13, 16–27]. Although SLE occurs predominantly in females, the incidence of SLE is low before puberty and after menopause (i.e., outside the reproductive ages) [32]. Sex difference in susceptibility is largest during the reproductive ages [33], which suggests that high endogenous estrogen concentrations may increase the risk for the development of SLE. Estrogens enhance B cell activation (e.g., immunoglobulin production including anti-ds-DNA), while they suppress T cell activity (e.g., proliferative response to mitogens and antigens, interleukin 2 production) [32].

Costenbader et al. [29] reported that menarche at a younger age (10 years old or younger vs. 12 years old: RR 2.1, 95% CI = 1.4–3.2) increased the risk for the development of SLE in the NHS 1976–2002 and the NHSII 1989–2003. In addition, they also reported that age at menarche was inversely associated with a risk for the development of SLE (vs. 12 years old: RR = 2.1 for 10 years or younger, RR = 1.2 for 11 years old, RR = 1.0 for 12 years old, 1.1 for 13 years old, and RR = 1.1 for 14 years old, and RR = 1.0 for 14 years old or older, p for trend = 0.02) [29]. These findings suggest that the exposure to high concentrations of endogenous estrogen at early age may increase the risk for the development of SLE.

On the other hand, Bernier et al. [30] reported that current use of combined oral contraceptives increased the risk of SLE (RR 1.54, 95% CI = 1.15–2.07), but past use of combined oral contraceptives did not increase the risk (RR 1.06, 95% CI = 0.85–1.33). In addition, they also reported that the risk of SLE increased with the dose of ethinyl estradiol (vs. nonusers: RR 1.42 for 30 μg or less, RR 1.63 for 31–49 μg, and RR 2.92 for 50 μg), while Costenbader et al. [29] reported that use of oral conceptive (vs. never: RR 1.5, 95% CI = 1.1–2.1) and use of postmenopausal hormones (vs. never: RR 1.9, 95 % CI = 1.2–3.1) increased the risk for development of SLE in the Nurses' Health Study. These findings suggest that use of exogenous estrogens may increase the risk for the development of SLE.

Costenbader et al. [29] also reported that postmenopausal women primary after surgical menopause (vs. premenopausal: RR 2.3, 95% CI = 1.2–4.5) and early age of menopause (younger than 47 years old vs. 53 years old and older: RR 2.2, 95% CI = 0.9–5.4) showed an increased risk for the development of SLE. In their study, most of females who developed SLE after menopause were those with surgical menopause (i.e., bilateral oophorectomy) and were more likely to have taken postmenopausal hormones [29]. The increased risk of developing SLE among postmenopausal females in their study may be partly explained by the use of postmenopausal hormones (RR 1.9, 95% CI = 1.2–3.1) [29] and the surgery (vs. no surgery: surgery without blood transfusion: OR 1.54, 95% CI = 1.05–2.26; surgery with blood transfusion: OR 4.46, 95% CI = 1.99–10.00) [34].

Ulff-Møller et al. [35] reported that live birth showed a decreased risk of SLE among Danish females (RR 0.74, 95% CI = 0.64–0.86), while Washio et al. [34] reported that live birth (OR 0.23, 95% CI = 0.09–0.59) decreased the risk of SLE and found a positive association between the risk of SLE and the number of living children delivered among Japanese females (vs. 0; OR 0.27 for one to two children, and OR 0.14 for three or more children, p for trend <0.01). On the other hand, Cooper et al. [36] could not find any meaningful association between the risk of SLE and number of live births. However, they found that breast-feeding was associated with a decreased risk of SLE (OR 0.6, 95% CI = 0.4–0.9) among females in the United States [36]. These findings suggest that lactation may play an important role in reducing the risk of SLE among women with live-born children because serum estrogen levels are usually at or below the lower range for the early follicular phase of the normal menstrual cycle during the lactation [37].

4.2 Tobacco smoking and alcohol drinking

Several researchers suggested that smoking increased the risk of SLE [38–42]. Ghaussy et al. [39] reported a significantly increased risk of SLE in both current and former smokers compared with never smokers (current smokers: OR 6.69, 95% CI = 2.59–17.28, former smokers: OR 3.62, 95% CI = 1.22–10.70) in the United States. On the other hand, others reported no association with smoking history (i.e., current, former, or never-smoker) and the risk of SLE in the United States [43, 44]. A meta-analysis by Costenbader et al. [45] revealed an increased risk of SLE among current smokers compared with nonsmokers (summary OR 1.50, 95% CI = 1.09–2.08).

The Kyushu Sapporo SLE study (i.e., the KYSS Study) was a hospital-based case-control study to evaluate nongenetic and genetic risk factors for the development of SLE among Japanese females [42]. All SLE patients fulfilled the American College of Rheumatology 1982 revised criteria for SLE [8]. In the KYSS study, Kiyohara et al. [46] reported that (1) compared with nonsmokers, smokers showed an increased risk of SLE (vs. nonsmokers: OR 2.49 for former smokers, and OR 3.06 for current smokers, p for trend <0.01). In addition, the risk of SLE increased with number of cigarettes smoked/day during peak smoking period (vs. 0/day: OR 2.77 for 1–19/day, and OR 3.29 for 20+/day, p for trend<0.01) [46]. Since hydrazine, a drug containing aromatic amines, is a known inducer of SLE [47], aromatic amines in cigarette smoke may partly explain the association between smoking and the risk of SLE.

Some studies suggested that alcohol consumption may decrease the risk of SLE [38, 40, 41]. Hardy et al. [38] reported a dose-response negative association between alcohol drinking and SLE risk (vs. 0 unit of alcohol: OR 0.73 for 1–2 units, OR 0.41 for 3–5 units, OR 0.47 for 6–10 units, and OR 0.30 for more than 10 units, p for trend <0.01). On the other hand, other studies failed to show an inverse association between alcohol drinking and SLE risk [37, 40]. A meta-analysis by Wang et al. [48] demonstrated that moderate alcohol drinking might have a protective effect on the development of SLE (vs. none: summary OR 0.73, 95% CI = 0.547–0.954). In the KYSS study, Kiyohara et al. [46] found a U-shape relationship between alcohol consumption and SLE risk among Japanese females (vs. 0 ml/week: OR 0.52, 95% CI = 0.31–0.86 for 1–70 ml/week, OR 0.38, 95% CI = 0.19–0.76 for 71–210 ml/week, and OR 0.67, 0.31–1.46 for 211 ml/week or more). These findings suggest that light to moderate alcohol consumption may decrease the risk of SLE.

Although there are potential biases associated with retrospective assessment of exposures and selection of cases and controls in a case-control study [49], Kiyohara et al. [46] reported that ever-smokers with drinking alcohol (OR 3.44, 95% CI = 2.03–5.82), nonsmokers without drinking alcohol (OR 2.56, 95% CI = 1.57–4.17), and ever-smokers without drinking alcohol (OR 6.98, 95% CI = 2.87–17.0) showed a greater risk of SLE than nonsmokers with drinking alcohol in Japanese women.

4.3 Occupational exposures and chemicals

Crystalline silica exposure is known to increase the risk of SLE [50, 51]. Finckh et al. [52] reported that exposure to silica for more than 1 year increased the risk of SLE (OR 4.3, 95% CI = 1.7–11.2). They also reported that the risk of SLE was associated with the duration of exposure to silica (vs. less than 1 year: OR 4.0 for 1–5 years, and OR 4.9 for more than 5 years, p for trend = 0.01) [52]. Parks et al. [53] reported a positive relationship between a history of silica exposure and SLE risk (vs. none: OR 1.6 for low, and OR 3.1 for medium or high, p for trend = 0.003).

On the other hand, Cooper et al. [54] reported that occupational silica exposure increased the risk of SLE among never-smokers (vs. no-silica exposure: OR 2.6, 95% CI = 1.2–5.7) but not among ever-smokers (vs. no-silica exposure: OR 0.99, 95% CI = 0.46–2.1), which suggests that smoking may play a more important role in the development of SLE than silica exposure.

Cooper et al. [43] reported that any use of permanent dyes increased the risk of SLE (OR 1.5, 95% CI = 1.0–2.2) in the United States. On the other hand, Sanchez-Guerrero et al. [44] failed to find a positive association between use of permanent hair dye and SLE risk (ever-users vs. never-users: OR 0.96, 95% CI = 0.63–1.47) in the Unites States.

4.4 Ultraviolet radiation exposure

Washio et al. [42] reported that walking increased the risk of SLE in Kyushu, southern Japan with a temperate climate (30 min/day or more vs. less than 30 min/day: OR 2.07, 95% CI = 1.14–3.76) but failed to increase the risk of SLE in Hokkaido, northern Japan with a subarctic climate (30 min/day or more vs. less than 30 min/day: OR 1.13, 95% CI = 0.46–2.79). In this study, walking may be a surrogate of staying outdoors with exposure to strong sunlight [42]. On the other hand, Cooper et al. [54] reported that outdoor work in the 12 months preceding diagnosis (OR 2.0, 95% CI = 1.0–3.8) increased the risk of SLE. In their study, a larger variation in the association between outdoor work and SLE risk was seen when examined within categories of sun reaction to midday sun (vs. none; OR 0.75 for tan or darken without burning, OR 2.7 for sunburn, and OR 7.9 for sunburn with blistering or rash) [54]. However, it is controversial whether ultraviolet (UV) radiation exposure itself plays a role in the development of SLE although UV radiation exposure may exacerbate preexisting SLE [50].

4.5 Family history

Family history of SLE [40, 55] as well as family history of connective tissue diseases/autoimmune diseases [40, 41, 55] is reported to increase the risk of SLE. Alarcón-Segovia et al. [56] reported that there was familial aggregation of SLE and of RA in SLE patients. These findings suggest that predisposing genes of autoimmune diseases as well as environmental risk factors sharing in family members may play a role in the development of autoimmune diseases including SLE.

4.6 Genetic susceptibility

It is widely accepted that SLE development requires environmental factors acting on a genetically predisposed individual. Studies of twin concordance are commonly used in epidemiology to estimate the role of genetics and the influence of environmental factors on disease susceptibility. Disease concordance is much higher in monozygotic twins (24–57%) than in dizygotic twins (2–5%),

suggesting that a genetic factor may play a role in the development of SLE [57, 58]. The genetic basis of SLE is very complex; it has been estimated that over 100 genes may be involved in SLE susceptibility [59], but it is difficult to predict how many genes contribute to SLE susceptibility. Exposure to reactive oxygen species (ROS) via cigarette smoking is thought to contribute to the development of SLE. ROS is considered to promote the autoimmune response [60]. The cytochrome P450 (CYP)1A1 and glutathione S-transferase (GST) M1 enzymes are critical for the functionalization of genotoxic substances in cigarette smoke. The CYP1A1 enzyme contributes to the phase I metabolic activation and formation of ROS, whereas the GSTM1 enzyme plays a critical role for phase II detoxification of activated carcinogens or ROS [61, 62]. Extensive studies have been performed on the possible associations between polymorphisms of *CYP1A1* and *GSTM1* and cancer susceptibility [63–65]. Similarly, the N-acetyltransferase (NAT) enzyme is involved in the metabolism and detoxification of cytotoxic and carcinogenic compounds as well as ROS [66]. It has been suggested that N-acetylation of polycyclic aromatic hydrocarbons (PAHs) by the NAT2 enzyme may be associated with ROS production [67]. ROS increase immunogenicity of DNA, LDL, and IgG, generating ligands for which autoantibodies show higher avidity [60]. Tumor necrosis factor r superfamily member 1B (TNFRSF1B) is a receptor for TNF-α and is considered to mediate various biological effects including generation of ROS and the subsequent intracellular proinflammatory signaling events [68]. Furthermore, cigarette smoking has been suggested to influence TNFRSF1B production [69, 70]. Representative functional polymorphisms of the *CYP1A1*, *GSTM1*, *NAT2*, and *TNFRSF1B* genes are *CYP1A1* rs464903, *GSTM1* deletion, *NAT2* genotypes determined by *NAT2**4, *5B, *6A, or *7B allele and *TNFRSF1B* rs1061622. Considering that exposure to ROS via cigarette smoking may be contributed to the development of SLE, it is important to study the association between SLE and the polymorphisms involved in metabolism of tobacco smoke and ROS production. We conducted candidate gene association studies (hypothesis-driven approach) of SLE in female Japanese subjects with special reference to the interaction between the polymorphisms involved in ROS production and cigarette smoking [71–74]. *CYP1A1* rs4646903 (OR of the CC genotype = 2.47, 95% CI = 1.28–4.78) [71] and *NAT2* genotypes (OR of the intermediate acetylator and slow acetylator genotypes combined = 2.34, 95% CI = 1.36–4.02) were significantly associated with SLE risk [72]. *TNFRSF1B* rs1061622 was marginally associated with an increased risk of SLE (OR of the G allele possession = 1.56, 95% CI = 0.99–2.47) [71]. There were significant additive interactions between smoking and any one of the following: *CYP1A1* rs4646903, *NAT2*, or *TNFRSF1B* rs1061622 [72–74]. Replication of findings is very important before any causal inference can be drawn. Testing replication in different populations is an important step. Future studies involving larger control and case populations, precisely and uniformly defined clinical classification of SLE and better exposure histories, will undoubtedly lead to a more thorough understanding of the role of the genetic polymorphisms involved in ROS production in SLE development.

5. Applications of findings in the epidemiological studies

Descriptive epidemiologic studies of SLE have been conducted not only in the Western countries (e.g., the United Kingdom, France, the United States, Canada) but also in Asian countries (e.g., China, South Korea, Japan). The prevalence of SLE provides useful information for the needs of health services for SLE patients. Information of the age- and sex-specific incidence and prevalence of SLE can be used to estimate the number of newly diagnosed SLE patients and the total number

of SLE patients in a community whose age and sex structure is known. On the other hand, the discrepancies of rates between different groups (e.g., different ethnic groups in the same country, different countries), which may be partly due to genetic factors as well as due to environmental factors [6], may give epidemiologists clues to plan epidemiological studies to determine a risk factor for SLE.

Observational studies such as case-control studies and cohort studies have been conducted to determine factors related to the development of SLE (i.e., risk factors, preventive factors) [49, 75]. After determining risk factors, preventive action will be started to control the level of exposure to a risk factor for SLE (i.e., reducing the risk of SLE) as well as to undergo a medical examination for the early detection of SLE for persons who are at special risk (e.g., silica [50–54]) (i.e., high risk strategy [76]). The size of relative risk/odds ratio indicates the strength of association between an exposure and a risk of SLE. For a public health perspective, however, the attributable risk of SLE is more important than the relative risk. The attributable risk is the difference in the risk of SLE between the exposed and the unexposed persons [49, 75]. The population attributable risk is the incidence of SLE in a population that is associated with an exposure to a risk factor, which is useful for determining the relative importance of exposures for the entire population [49, 75]. When the proportion of exposed persons is large, the population attribute risk is high even if the relative risk is small. More cases of SLE may develop in a large number of persons who are at a small risk than in the small number who are at high risk.

Smoking is an avoidable risk factor for SLE [38–42, 45] as well as for cancer [77] and cardiovascular diseases [78]. Therefore, antismoking education for both smokers and nonsmokers throughout lifetime (i.e., population strategy [76]) is important to reduce the incidence of SLE as well as the incidence of cancer and cardiovascular diseases in the general population.

6. Summary

The incidence and prevalence of SLE vary with sex, age, ethnicity, and the way how to detect SLE patients (e.g., case definition). SLE is more common in women than men across all age groups, and this female predominance is especially noteworthy during the reproductive ages [28], which suggests that female sex hormones may play an important role in the development of SLE.

A lower incidence and prevalence of SLE has been constantly observed in White People than in Black People [12, 17, 18] as well as Asian/Pacific Islanders [6, 17, 18] in the United States, while the incidence and prevalence of SLE is lower in White People than in Black African, Black Caribbean, and Indian [16]. The discrepancies of rates between ethnic groups are in part due to genetic factors as well as due to environmental factors such as smoking and dietary habits [7].

There are worldwide differences in the incidence and prevalence of SLE [79]. In addition to genetic factors and environmental factors, the way to detect SLE patients (e.g., case definition) is an important factor, which influences the incidence and prevalence of SLE. Ighe et al. [15] reported that the SLICC case definition of SLE yielded higher incidence and prevalence estimates than the ACR-97 case definition.

In this chapter, we introduce factors related to the development of SLE as well as incidence and prevalence of SLE. Among the reproductive issues, menarche at a younger age [29], use of contraceptive [29, 30], and use of postmenopausal hormones [29] increase the risk of SLE, while breast-feeding is associated with a decreased risk of SLE. Among environmental factors, tobacco smoking increases the risk of SLE [38–42, 46], while light to moderate alcohol drinking decreases

the risk of SLE [46]. On the other hand, the exposure to crystalline silica [50, 51], silica [52, 53], strong sunlight [42, 54], and ultraviolet radiation [50] increase the risk of SLE. Among genetic factors, *CYP1A1* rs4646903 and *NAT2* genotypes are associated with an increased risk of SLE, while *TNFRSF1B* rs1061622 is suggested to increase the risk of SLE [71–74]. In order to reduce the risk of SLE, we should reduce the exposure to avoidable risk factors such as smoking, contraceptives, crystalline silica, silica, strong sunlight, or ultraviolet radiation.

Author details

Masakazu Washio[1], Chikako Kiyohara[2*] and Akiko Ohta[3]

1 Department of Community Health and Clinical Epidemiology, St. Mary's College, Kurume City, Fukuoka, Japan

2 Department of Preventive Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka City, Fukuoka, Japan

3 Division of Public Health, Department of Social Medicine, Faculty of Medicine, Saitama Medical University, Moroyama-machi, Saitama, Japan

*Address all correspondence to: chikako@phealth.med.kyushu-u.ac.jp

References

[1] Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Parks CG, Gilkeson GS. Hormonal, environmental, and infectious risk factors for developing systemic lupus erythematosus. Arthritis and Rheumatism. 1998;**41**:1714-1724

[2] Wallace DJ. The clinical presentation of systemic lupus erythematosus. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2002. pp. 621-628

[3] Nakatani H. The advance and features of intractable diseases control as the health policy of the Japanese Ministry of Health and Welfare. In: Ohno Y, Tanaka H, Nakatani H, Kurokawa K, Saito H, editors. The Latest Information about Intractable Diseases, Including Epidemiology, Clinical Medicine and Care for Patients. Tokyo: Nanzando; 2000. pp. 3-27. (In Japanese)

[4] Washio M, Inaba Y. Introduction of epidemiological studies of "Nanbyo", current topics in environmental health and preventive medicine. In: Washio M, Kobashi G, editors. Epidemiological Studies of Specific Rare and Intractable Disease. Singapore: Springer Nature Singapore Pte Ltd; 2019. pp. 1-13. ISBN: 978-981-13-1095-9

[5] Ohta A, Nagai M, Nishina M, Tomimitsu H, Kohsaka H. Age at onset and gender distribution of systemic lupus erythematosus, polymyositis/dermatomyositis, and systemic sclerosis in Japan. Modern Rheumatology. 2013;**23**:759-764

[6] Serdula MK, Rhoads GG. Frequency of systemic lupus erythematosus in different ethnic groups in Hawaii. Arthritis and Rheumatism. 1979;**22**:328-333

[7] Lim SS, Drenkard C. The epidemiology of lupus. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus and Related Syndrome. 8th ed. Philadelphia: Elsevier, Saunders; 2013. pp. 8-24

[8] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis and Rheumatism. 1982;**25**:1271-1277

[9] Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis and Rheumatism. 1997;**40**:1725

[10] Voss A, Green A, Junker P. Systemic lupus erythematosus in Denmark: Clinical and epidemiological characterization of a county-based cohort. Scandinavian Journal of Rheumatology. 1998;**27**(2):98-105

[11] Uramoto KM, Michet CJ Jr, Thumboo J, Sunku J, O'Fallon WM, Gabriel SE. Trends in the incidence and mortality of systemic lupus erythematosus, 1950-1992. Arthritis and Rheumatism. 1999;**42**(1):46-50

[12] Lim SS, Bayakly AR, Helmick CG, Gordon C, Easley KA, Drenkard C. The incidence and prevalence of systemic lupus erythematosus, 2002-2004: The Georgia lupus registry. Arthritis & Rhematology. 2014;**66**(2):357-368

[13] Izmirly PM, Wan I, Shal S, Buyon JP, Belmont HM, Salmon JE, et al. The incidence and prevalence of systemic lupus erythematosus in New York County (Manhattan), New York: The Manhattan Lupus Surveillance Program. Arthritis & Rhematology. 2017;**69**(10):2006-2017

[14] Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and

validation of the systemic. Lupus international collaborating clinics classification criteria for systemic lupus erythematosus. Arthritis and Rheumatism. 2012;**64**(8):2677-2686

[15] Ighe A, Dahlström Ö, Skogh T, Sjöwall C. Application of the 2012 systemic lupus international collaborating clinics classification criteria to patients in a regional Swedish systemic lupus erythematosus register. Arthritis Research & Therapy. 2015;**17**:3. DOI: 10.1186/s13075-015-0521-9

[16] Rees F, Doherty M, Grainge M, Davenport G, Lanyon P, Zhang W. The incidence and prevalence of systemic lupus erythematosus in the UK, 1999-2012. Annals of the Rheumatic Diseases. 2016;**75**:136-141

[17] Somers EC, Marder W, Cagnoli P, Lewis EE, DeGuire P, Gordon C, et al. Population-based incidence and prevalence of systemic lupus erythematosus: The Michigan lupus epidemiology and surveillance program. Arthritis & Rhematology. 2014;**66**(2):369-378

[18] Dall'Era M, Cisternas MG, Snipes K, Herrinton LJ, Gordon C, Helmick CG. The incidence and prevalence of systemic lupus erythematosus in San Francisco County, California, the California lupus surveillance project. Arthritis & Rhematology. 2017;**69**(10):1996-2005

[19] Barnabe C, Joseph L, Belisle P, Labrecque J, Edworthy S, Barr SG, et al. Prevalence of systemic lupus erythematosus and systemic sclerosis in the first nations population of Alberta, Canada. Arthritis Care and Research (Hoboken). 2012;**64**(1):138-143

[20] Somer EC, Thomas SL, Smeeth L, Schoonen WM, Hall AJ. Incidence of systemic lupus erythematosus in the United Kingdom, 1990-1999. Arthritis and Rheumatism. 2007;**57**(4):612-618

[21] Arnaud L, Fagot JP, Mathian A, Paita M, Fagot-Campagna A, Amoura Z. Prevalence and incidence of systemic lupus erythematosus in France: A 2010 nation-wide population-based study. Autoimmunity Reviews. 2014;**13**(11):1082-1089

[22] Zou YF, Feng CC, Zhu JM, Tao JH, Chen GM, Ye QL, et al. Prevalence of systemic lupus erythematosus and risk factors in rural areas of Anhui Province. Rheumatology International. 2014;**34**(3):347-356

[23] Yu K-H, See L-C, Kuo C-F, Chou I-J, Chou M-J. Prevalence and incidence in patients with autoimmune rheumatic diseases: A nationwide population-based study in Taiwan. Arthritis Care and Research. 2013;**65**(2):244-250

[24] Shim J-S, Sung Y-K, Joo YB, Lee H-S, Bae S-C. Prevalence and incidence of systemic lupus erythematosus in South Korea. Rheumatology International. 2014;**34**(7):909-917

[25] Yamamoto R, Nishigoori T, Shimizu H, Hisamichi S, Fukao A, Komatsu M. Estimated incidence of intractable diseases. Japanese Journal of Public Health. 1986;**33**(2):87-90. (In Japanese)

[26] Ohno Y, Kawamura T, Tamakoshi A, Wakai K, Aoki R, Kojima M, et al. Epidemiology of intractable diseases in Japan. Journal of Epidemiology. 1996;**6**(4):S99-S109

[27] Iseki K, Miyasato F, Oura T, Uehara H, Nishime K, Fukiyama K. An epidemiologic analysis of end-stage lupus nephritis. American Journal of Kidney Diseases. 1994;**23**(4):547-554

[28] Rus V, Hochberg MC. The epidemiology of systemic lupus erythematosus. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus. 6th ed. Philadelphia: Lippincott Williams and Wilkins; 2002. pp. 65-83

[29] Costenbader KH, Fekanich D, Stampfer MJ, Karlson EW. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. Arthritis and Rheumatism. 2007;**56**:1251-1262

[30] Bernier MO, Mikaeloff Y, Hudson M, Suissa S. Combined oral contraceptive use and the risk of systemic lupus erythematosus. Arthritis and Rheumatism. 2009;**61**:476-481

[31] Lu L-J, Wallace DJ, Ishimori ML, Scofield RH, Weisman MH. Male systemic lupus erythematosus: A review of sex disparities in this disease. Lupus. 2010;**19**:119-129

[32] Mok CC, Lau CS. Pathogenesis of systemic lupus erythematosus. Journal of Clinical Pathology. 2003;**56**:481-490

[33] Chakravarty EF. Reproductive and hormonal issues in women with autoimmune diseases. In: Wallace DJ, Hahn BH, editors. Dubois' Lupus Erythematosus and Related Syndrome. 8th ed. Philadelphia: Elsevier Saunders; 2013. pp. 473-483

[34] Washio M, Takahashi H, Kobashi G, Kiyohara C, Tada Y, Asami T, et al. Risk factors for development of systemic lupus erythematosus among Japanese females: Medical history and reproductive factors. International Journal of Rheumatic Diseases. 2017;**20**(1):76-83

[35] Ulff-Møller CJ, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Reproductive factors and risk of systemic lupus erythematosus: Nationwide cohort study in Denmark. The Journal of Rheumatology. 2009;**36**(9):1903-1909

[36] Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS. Hormonal and reproductive risk factors for development of systemic lupus erythematosus: Results of a population-based, case-control study. Arthritis and Rheumatism. 2002;**46**(7):1830-1839

[37] Said S, Johansson ED, Gemzell C. Serum estrogens and progesterone after normal delivery. The Journal of Obstetrics and Gynaecology of the British Commonwealth. 1973;**80**(6):542-525

[38] Hardy CJ, Palmer BP, Muir KR, Sutton AJ, Powell RJ. Smoking history, alcohol consumption, and systemic lupus erythematosus: A case-control study. Annals of the Rheumatic Diseases. 1998;**57**:451-455

[39] Ghaussy NO, Sibbitt WL Jr, Qualls CR. Cigarette smoking, alcohol consumption, and the risk of systemic lupus erythematosus: A case-control study. The Journal of Rheumatology. 2001;**28**:2449-2453

[40] Bengtsson AA, Rylander L, Hangmar L, Nived O, Sturfelt G. Risk factors for developing systemic lupus erythematosus : A case-control study in southern Sweden. Rheumatology. 2002;**41**:563-571

[41] Nagata C, Fujita S, Hirotoshi I, Kurosawa Y, Kobayashi M, Motegi K, et al. Systemic lupus erythematosus: A case-control epidemiologic study in Japan. International Journal of Dermatology. 1995;**34**:333-337

[42] Washio M, Horiuchi T, Kiyohara C, Kodama H, Tada Y, Asami T, et al. Smoking, drinking, sleeping habits, and other lifestyle factors and the risk of systemic lupus erythematosus in Japanese females: Findings from the KYSS study. Modern Rheumatology. 2006;**16**(3):143-150. DOI: 10.1007/s10165-006-0474-6

[43] Cooper GS, Dooley MA, Treadwell EL, St Clair EW, Gilkeson GS. Smoking and use of hair treatments in relation to risk of developing systemic lupus

erythematosus. The Journal of Rheumatology. 2001;**28**:2653-2656

[44] Sanchez-Guerrero J, Karlson EW, Colditz GA, Hunter DJ, Speizer FE, Liang MH. Hair dye use and the risk of developing systemic lupus erythematosus: A cohort study. Arthritis and Rheumatism. 1996;**39**:657-662

[45] Costenbader KH, Kim DJ, Peerzada J, Lockman S, Nobles-Knight D, Petri M, et al. Cigarette smoking and the risk of systemic lupus erythematosus: A meta-analysis. Arthritis and Rheumatism. 2004;**50**(3):849-857

[46] Kiyohara C, Washio M, Horiuchi T, Asami T, Ide S, Atsumi T, et al. Cigarette smoking, alcohol consumption, and risk of systemic lupus erythematosus: A case-control study in a Japanese population. The Journal of Rheumatology. 2012;**39**(7):1363-1370

[47] Reidenberg MM, Durant PJ, Harris RA, De Boccardo G, Lahita R, Stenzel KH. Lupus erythematosus-like disease due to hydrazine. The American Journal of Medicine. 1983;**75**:365-370

[48] Wang J, Pan HF, Ye DQ, Su H, Li XP. Moderate alcohol drinking might be protective for systemic lupus erythematosus: A systematic review and meta-analysis. Clinical Rheumatology. 2008;**27**(12):1557-1563

[49] Beaglehole R, Bonita R, Kjellström T. Basic Epidemiology. Genova: World Health Organization; 1993

[50] Barbhaiya M, Costenbader KH. Environmental exposures and the development of systemic lupus erythematosus. Current Opinion in Rheumatology. 2016;**28**(5):497-505

[51] Parks CG, De Roos AJ. Pesticides, chemical and industrial exposures in relation to systemic lupus erythematosus. Lupus. 2014;**23**(6):527-536

[52] Finckh A, Cooper GS, Chibnik LB, Costenbader KH, Watts J, Pankey H, et al. Occupational silica and solvent exposures and risk of systemic lupus erythematosus in urban women. Arthritis and Rheumatism. 2006;**54**(11):3648-3654

[53] Parks CG, Cooper GS, Nylander-French LA, Sanderson WT, Dement JM, Cohen PL, et al. Occupational exposure to crystalline silica and risk of systemic lupus erythematosus: A population-based, case–control study in the southeastern United States. Arthritis and Rheumatism. 2002;**46**(7):1840-1850

[54] Cooper GS, Wither J, Bernatsky S, Claudio JO, Clarke A, Rioux JD, et al. Occupational and environmental exposures and risk of systemic lupus erythematosus: Silica, sunlight, solvents. Rheumatology. 2010;**49**:2172-2180

[55] Tada Y, Washio M, Horiuchi T, Kiyohara C, Takahashi H, Kobashi G, et al. Influence of medical history in parents or siblings on the development of systemic lupus erythematosus among Japanese females. International Medical Journal. 2016;**23**(5):466-469. ISSN: 1341-2051

[56] Alarcón-Segovia D, Alarcón-Riquelme ME, Cardiel MH, Caeiro F, Massardo L, Villa AR, et al. Familial aggregation of systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune diseases in 1,177 lupus patients from the GLADEL cohort. Arthritis and Rheumatism. 2005;**52**:1138-1147

[57] Jarvinen P, Aho K. Twin studies in rheumatic diseases. Seminars in Arthritis and Rheumatism. 1994;**24**(1):19-28

[58] Deapen D, Escalante A, Weinrib L, Horwitz D, Bachman B, Roy-Burman P, et al. A revised estimate

of twin concordance in systemic lupus erythematosus. Arthritis and Rheumatism. 1992;**35**(3):311-318

[59] Tsao BP. Update on human systemic lupus erythematosus genetics. Current Opinion in Rheumatology. 2004;**16**(5):513-521

[60] Griffiths HR. Is the generation of neo-antigenic determinants by free radicals central to the development of autoimmune rheumatoid disease? Autoimmune Reviews. 2008;**7**(7):544-549

[61] Nebert DW, Dalton TP. The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. Nature Reviews. Cancer. 2006;**6**:947-960

[62] Hayes JD, Flanagan JU, Jowsey IR. Glutathione transferases. Annual Review of Pharmacology and Toxicology. 2005;**45**:51-88

[63] Masson LF, Sharp L, Cotton SC, Little J. Cytochrome P-450 1A1 gene polymorphisms and risk of breast cancer: A HuGE review. American Journal of Epidemiology. 2005;**161**:901-915

[64] Castelao JE, Yuan JM, Skipper PL, Tannenbaum SR, Gago-Dominguez M, Crowder JS, et al. Gender- and smoking-related bladder cancer risk. Journal of the National Cancer Institute. 2001;**93**:538-545

[65] Parl FF. Glutathione S-transferase genotypes and cancer risk. Cancer Letters. 2005;**221**:123-129

[66] Unal M, Tamer L, Dogruer ZN, Yildirim H, Vayisoglu Y, Camdeviren H. N-acetyltransferase 2 gene polymorphism and presbycusis. Laryngoscope. 2005;**115**:2238-2241

[67] Kim WJ, Lee HL, Lee SC, Kim YT, Kim H. Polymorphisms of N-acetyltransferase 2, glutathione S-transferase mu and theta genes as risk factors of bladder cancer in relation to asthma and tuberculosis. The Journal of Urology. 2000;**164**:209-213

[68] Garg AK, Aggarwal BB. Reactive oxygen intermediates in TNF signaling. Molecular Immunology. 2002;**39**:509-517

[69] Fernandez-Real JM, Broch M, Vendrell J, Ricart W. Smoking, fat mass and activation of the tumor necrosis factor-alpha pathway. International Journal of Obesity and Related Metabolic Disorders. 2003;**27**:1552-1556

[70] D'Hulst AI, Bracke KR, Maes T, De Bleecker JL, Pauwels RA, Joos GF, et al. Role of tumour necrosis factor-alpha receptor p75 in cigarette smoke-induced pulmonary inflammation and emphysema. The European Respiratory Journal. 2006;**28**:102-112

[71] Horiuchi T, Washio M, Kiyohara C, Tsukamoto H, Tada Y, Asami T, et al. Combination of TNF-RII, CYP1A1 and GSTM1 polymorphisms and the risk of Japanese SLE: Findings from the KYSS study. Rheumatology (Oxford). 2009;**48**:1045-1049

[72] Kiyohara C, Washio M, Horiuchi T, Tada Y, Asami T, Ide S, et al. Cigarette smoking, N-acetyltransferase 2 polymorphisms and systemic lupus erythematosus in a Japanese population. Lupus. 2009;**18**:630-638

[73] Kiyohara C, Washio M, Horiuchi T, Tada Y, Asami T, Ide S, et al. Cigarette smoking, STAT4 and TNFRSF1B polymorphisms, and systemic lupus erythematosus in a Japanese population. The Journal of Rheumatology. 2009 Oct;**36**(10):2195-2203

[74] Kiyohara C, Washio M, Horiuchi T, Asami T, Ide S, Atsumi T, et al. Risk modification by CYP1A1 and GSTM1 polymorphisms in the association of

cigarette smoking and systemic lupus erythematosus in a Japanese population. Scandinavian Journal of Rheumatology. 2012;**41**(2):103-109

[75] Porta M, Greenland S, Last JM. A Dictionary of Epidemiology. 5th ed. Oxford: Oxford University Press; 2008

[76] Geoffrey R. The Strategy of Preventive Medicine. Oxford: Oxford University Press; 1992. ISBN: 0-19-262486-5

[77] Gajalakshmi CK, Jha P, Ranson K, Nguyen S. In: Jha P, Chalouplca F, editors. Global Patterns of Smoking and Smoking-Attributable Mortality, Tobacco Control in Developing Countries. New York: Oxford University Press; 2000. pp. 11-39

[78] Jamrozik K. Tobacco and cardiovascular disease. In: Boyle P, Gray N, Henningfield J, Seffrin J, Zatonski W, editors. Tobacco and Public Health: Science and Policy. New York: Oxford University Press; 2004. pp. 549-576. ISBN: 0-19-852687-3

[79] Rees F, Doherty M, Grainge M, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: A review of epidemiological studies. Rheumatology. 2017;**56**:1945-1961

Chapter 3

A Spontaneous Mouse Model of Lupus: Physiology and Therapy

Gabriela Tejon, Yessia Hidalgo, Maria Rosa Bono and Mario Rosemblatt

Abstract

Spontaneous models of lupus were recognized four decades ago beginning in the early 1960s with the NZB/NZW F1 (NZB/W F1) mouse, an F1 hybrid between the New Zealand Black (NZB) and New Zealand White (NZW) mice. Although the parental strains display limited autoimmunity, the NZB/W F1 develops severe lupus-like features similar to that of human lupus patients. Here, we will address the genetic characteristics of the model and discuss its main characteristics such as the presence of serum antinuclear autoantibodies (ANA) including anti-dsDNA, mild vasculitis, and the development of immune complex-mediated glomerulonephritis. Similar to human lupus, the disease develops primarily in female mice after six months of age, with a lesser percentage and severity in male mice. The relation of this phenomenon will be examined in the context of estrogen levels. The participation of both innate and adaptive immunity will be addressed as well as the contribution of both T and B cells in the development of the clinical aspects of the disease. We will focus on the use of the model as a valuable tool for elucidating the pathogenic mechanisms of the disease, as well as its use as preclinical testing of therapeutic for human use.

Keywords: lupus, mouse model, histopathology, autoreactive cells and antibodies, genetics, sex

1. Introduction

Autoimmune diseases are generally defined by the existence of autoantibodies and the presence of autoreactive T and B lymphocytes. More than 80 different autoimmune disorders have been described, including systemic lupus erythematosus (SLE). Animal models of human diseases are an invaluable tool for defining pathogenic mechanisms, finding novel therapeutic targets, and testing new therapies. These models have the advantage of having a shorter lifetime, a characteristic that allows to study the full cycle of the disease and to test for the possible therapies in much shorter period. Although using animal models may have some disadvantages due to the obvious genetic and physiological differences with humans, they have been an invaluable tool to study human diseases, especially in autoimmunity. Although the exact etiology of SLE has not yet been identified, there is a consensus that numerous factors such as genetics, environment, and hormonal aspects are involved in the development of this disease. Several mouse models resemble specific elements of the human disease and have been employed to understand the cellular and genetic treats linked to SLE susceptibility. Most of them, share in common, the development of glomerulonephritis and

Spontaneous models of lupus					
	Generation	**Autoantibodies**	**Sex Bias**	**Main clinical manifestation**	**Age for 50% Mortality (months)**
NZB/NZWF1	New Zealand Black crossed with the New Zealand White mouse	Anti-dsDNA , anticardiolipin, rheumatoid factors, cryoglobulin, gp70, RNA polymerase I, RNA, ubiquitin, helicase.	Develops primarily in females with lesser percentage and severity in male mice.	Splenomegaly, mild lymphadenopathy, hypergammaglobulinemia, glomerulonephritis, mild vasculitis and mild leukopenia	Female: 9 months of age Male: 15 months of age
MRL/lpr	Intercross of four different strains of mice: LG/J, AKR/J, C3H/HeDi, and C57BL/6.	Anti-dsDNA , anticardiolipin, rheumatoid factors, cryoglobulin, gp70, albumin, transferrin, La, Ro, Su, ribosome P, Sm, S10 RNA polymerase I, laminin, collagen, ubiquitin, mitochondria, circulating immune complexes.	More prevalent and accelerated in females, but not as prominent as in B/W.	Splenomegaly, lymphadenopathy, arthritis, cerebritis (Cognitive dysfunction), skin rash, vasculitis and nephritis	6 months of age
BXSB	Backcross between a C57BL/6 (B6) female and a satin beige (SB/Le) male	anti-dsDNA , cryoglobulin, gp70 albumin, transferrin	Only occurs in male mice	Glomerulonephritisis	5 months of age
Induced/accelerated models of lupus					
Pristane-induced	Intraperitoneally injection of pristane into normal mouse strain like BALB/c mice	Anti-RNP, anti-DNA, Anti-Sm, anti-ribosomal P and anti-histone.	More severe in females than in males, at least in SJL strain.	Glomerulonephritis, arthritis, anemia and serositis (strain dependent).	
Graft-versus-host (GVH) disease	Injections of donor lymphocytes into a semi-allogenic recipient	AutoAb	Female	Immune complex nephritis.	

Table 1.
Main mouse models used to study lupus.

autoantibodies against autoantigens. In **Table 1**, we summarize the principal characteristics of the most extensively studied mouse strains of both spontaneous and induced murine lupus models. Additionally, there are genetically modified mouse models in which researchers inactivate, express, or overexpress a gene product or protein to recognize their single role in lupus and immunity in general such as transgenic-induced lupus and gene knockout-induced lupus [1–3]. In this chapter, we will refer in detail to the NZB/W F1 mice, which are the oldest classic spontaneous models of lupus used to study, on the one hand, the numerous susceptibility loci from which several candidate genes have emerged. Also, it has allowed to address important issues such as physiological aspects of the disease, antibody specificities, the role of antigen-presenting cells, the participation of B and T lymphocytes, and drug responses in many preclinical studies. This model was generated by the cross between the NZB and NZW strains. Both NZB and NZW display limited autoimmunity, as will be discussed here, while the NZB/W F1 hybrids develop severe lupus-like phenotypes resembling that of lupus patients. The purpose of this chapter is to summarize the contributions and significant advances in the understanding of lupus pathogenesis by the use of the NZB/W F1 murine model.

2. Histopathology characteristics of NZB/W F1 mice

In pre-autoimmune NZB/W F1 mice, *in vivo* expression of IFN-α precipitates the autoimmune process and kidney damage, leading to premature death from severe immune complex glomerulonephritis. This fact does not happen in non-autoimmune BALB/c mice. These findings support the notion that sustained IFN-α production in susceptible individuals may be sufficient to generate all the characteristics of SLE [4]. Interestingly, Liu et al. demonstrated that IFN-α accelerates murine systemic lupus erythematosus in NZB/W mice in a T cell-dependent manner [5].

The major cause of death in the NZB/W F1 female is chronic glomerulonephritis with heavy mesangial deposits before 5 months of age, tubular cast formation, proliferation of glomerular cells, prominent crescent formation, and a significant periglomerular and interstitial monocytic infiltrate. Extraglomerular renal deposits of IgG2a and C3 are present in the peritubular tissue and arterioles, and increase in frequency with age.

Diseased mice develop splenomegaly and progressive thymic cortical atrophy that begins very early in the disease and results in nearly complete loss of the thymic cortex as the disease progresses. In many mice, the loss of cortex is accompanied by medullary atrophy. Additionally, females have lymphoid hyperplasia with nodes rarely exceeding 2–3 times the average size [6].

3. Serologic characteristics of NZB/W F1 mice

Interestingly very early, it was reported that repeated administration of dsDNA or ssDNA to NZB/W F1 mice has a tolerogenic and long-lasting effect in this strain of mice that otherwise are susceptible to developing lupus [7]. Autoimmune-prone NZB mice mainly produce anti-DNA antibodies IgM and develop a mild SLE. NZB/W F1 females develop a fulminant SLE at 6–9 months associated with a decrease in IgM and an increase in anti-DNA IgG antibodies. These results helped to elucidate the role of the H-2 complex in the anti-DNA antibody production, leading to the conclusion that the production of IgG anti-DNA antibodies observed in NZB/W F1 hybrid mice is restricted to the H-2d/H-2z heterozygous mice [8].

NZB/W F1 mice present high levels of circulating autoantibodies. Antibody-secreting cells (ASCs) from these mice produce antinuclear antibody (ANA) and anti-dsDNA predominantly, the majority of them being the IgG2a and IgG3 classes [3, 5, 9]. NZB/W F1 mice also produce other extractable nuclear antigens (ENA) autoantibodies such as anti-small nuclear ribonucleoprotein (snRNP) and anti-heterogeneous nuclear ribonucleoproteins (hnRNP) [10]. All these autoantibodies form immune complexes that are deposited in different organs like liver, kidney, and skin. Moreover, Brick et al. have described the presence of anti-histone antibodies in the serum of autoimmune NZB/NZW F1 mice and in MRL/lpr mice [11]. On the other hand, dietary fat affects antibody levels to lipids and cardiolipin in autoimmune-prone NZB/W F1 mice. Antibodies to cardiolipin have been reported to play an important role in thrombus formation and an increase in the rate of abortions, both in human lupus patients and in murine lupus [12].

CD5+ B-1 cells have attracted much attention, because of their involvement in both autoimmunity and B cell-type chronic lymphocytic leukemia (B-CLL). It has been demonstrated that elimination of B-1 cells prevents autoimmune symptoms in autoimmune-prone mice [13]. CD5+ B cells seem to be the precursors of CD5- anti-DNA IgG antibody-producing B cells in autoimmune-prone NZB/W F1 mice [14]. However, whether B-1 cells in the peritoneum are generally involved in the pathogenesis of the autoimmune disease remains controversial.

4. Cellular abnormalities

Systemic lupus erythematosus (SLE) produces alterations in the organism that affect cells of the innate and adaptive immune systems. In this section, we will

summarize the modifications described in diseased NZB/W F1 mice in different immune cell populations.

4.1 Dendritic cells

Dendritic cells (DCs) are the cellular sentinels of the organism, important orchestrators of immune responses, and key components in fine-tuning the balance between tolerance and immunity.

Two major subsets of DCs are described: conventional DCs (cDCs) and plasmacytoid DCs (pDCs), although other subsets of DCs have been described from DCs generated from bone marrow cultures [15]. Tissue-derived pDCs are considered to be the major IFN-α source in SLE; however, diseased NZB/W F1 mice show an increase in the frequency and absolute numbers of both cDCs and pDCs in spleen and blood compared to healthy mice. Also, compared to healthy mice, diseased mice present alterations in both types of DCs since they display an abnormal phenotype characterized by an overexpression of the co-stimulatory molecules CD80, CD86, PD-L1, and PD-L2. Homing experiments demonstrate that DCs from lupus-diseased mice migrate preferentially to the spleen compared to DCs from control mice. This preferential recruitment and retention of DCs in the spleen are related to altered expression of different chemokine and chemokine receptors on both DCs and spleen stromal cells [16]. Recently, pDCs from spleen and bone marrow have been compared in several models of lupus-prone mice without clear results concerning the role of pDC in the development of lupus [17].

In NZB/W F1 mice, the spleen is the principal organ, where nucleosome-specific T cells are stimulated. Splenic antigen-presenting cells, including macrophages, contribute significantly to the production of autoantibodies and in the development of the disease [18]. On the other hand, anti-apoptotic molecules such as Bcl-2 inhibitors selectively kill pDCs, but not cDCs, reducing IFN-α production [19].

4.2 Macrophages

Macrophages are professional antigen-presenting cells and play an essential role in the activation of the adaptative immune response. Macrophages usually eliminate circulating apoptotic bodies and pathogens. Macrophages from diseased NZB/W F1 lupus mice have reduced phagocytic capacity. The impaired ability of resident peritoneal macrophages from lupus-prone mice to engulf apoptotic cells has been demonstrated by *in vivo* and *in vitro* cell clearance assays [20, 21]. Some studies have shown defective Fc-mediated phagocytosis by peritoneal macrophages [22] making more autoantigens available that favor an autoimmune response. In this regard, it was shown that spleen F4/80^{high} macrophages could present autoantigen efficiently to T cells, thus giving help to autoantibody-producing B cells in lupus-prone mice [18].

F4/80^{high} macrophages reside in healthy kidneys. In NZB/W F1, there is an increasing number of macrophages during nephritis. However, these macrophages do not show a pro-inflammatory (M1) or anti-inflammatory (M2) phenotype upon cytokine stimulation. Instead, they acquired a mixed functional phenotype that resembles gut F4/80^{high} macrophages constitutively activated [23]. Macrophages from diseased NZB/W F1 mice differ in the expression of some inflammatory genes, chemokine receptors, and TLRs, which are consistent with their heterogeneity and variability in renal location, further supporting the idea that ineffective macrophage function may contribute to glomerulonephritis in NZB/W F1 mice.

Macrophages produce a broad array of cytokines that can affect the immune response. For example, macrophages from peritoneal cavity upon stimulation with

DNA secrete high amounts of IL-6 and TNF-α [24], two cytokines that participate in B cell proliferation and function. Very early, it was reported that IL-6 secretion by peritoneal and not by spleen macrophages have an active role in the production of anti-DNA autoantibodies in NZB/W F1 mice [25].

4.3 T cells

In the NZB/W F1 lupus mice, spleen $CD4^+$ T cells exhibit an activated phenotype characterized by high expression of PD-1, CD25, CD69 and increased secretion of IFN-γ and IL-10 [16, 26]. The primary function of T cells in lupus is to help B cells in the production of autoantibodies [27], thus, avoiding the interaction between T and B cells may decrease the signs of the disease. Treatment with an anti-CD4 monoclonal antibody dramatically reduced glomerular immunoglobulin, complemented deposition, and diminished lymphocytic infiltration and vasculitis in the kidneys [28]. CD28 blockade decreased the production of anti-ds DNA autoantibody, prevented the development of lupus nephritis, and prolonged animal survival [29].

Regulatory $CD4^+$ T cells (Tregs) are essential players in the maintenance of peripheral immune tolerance. Usually, Tregs suppress the activity of specific T helper (Th) cells, but in NZB/W F1 mice, a homeostatic state of imbalance between regulatory and effector T cells is produced due to a decrease of IL-2, an essential cytokine for the maintenance of Tregs [30]. On the other hand, the levels of the adipocytokine leptin are elevated in diseased mice and correlate with the production of autoantibodies and renal disease. Although leptin can promote effector T cell responses to self-antigens, it also inhibits Treg activity [31]. On the other hand, Likuni et al. demonstrated that Tregs could directly suppress B cells in NZB/W F1 lupus mice through cell-to-cell contact-mediated mechanisms, thus directly regulating auto-antibody-producing B cells, including those B cells that increase in number during active disease [32].

Follicular helper T cells are CD4+ T cells population that supports the activation and differentiation of previously class-switched B cells to long-lived antibody-secreting plasma cells. Recent reports show that follicular helper T cells contribute to the pathogenesis of lupus through the ICOS/ICOSL pathway in NZB/W F1 mice [33]. Also, the activation through the Ox40/Ox40L pathway increases the number of follicular helper T cells and promotes cellular and humoral autoimmune responses in NZB/W F1 mice [34]. Interestingly, Cortini et al. showed that, reciprocally, B cells support the follicular helper T cells development in NZB/W F1 mice through the OX40L expression on B cells [35].

Although $CD8^+$ T cells have not been directly implicated in SLE, sick NZB/W F1 mice show an impaired expansion of $CD8^+$ T cells, as well as the acquisition of memory, secretion of cytokine, and suppression of autoimmunity [36].

4.4 B cells

Participation of B cells in lupus implicates several of its cellular functions. Besides the secretion of autoantibody against a panoply of antigens, B cells contribute in other ways to the pathogenesis of lupus, including antigen presentation to T cells, follicular helper T cell differentiation, and cytokine secretion. Although the phenotype of resting B cells isolated from NZB/W F1, and non-autoimmune mice do not show significant differences, B cells from lupus mice are hyper-responsive to T cell-derived stimuli *in vitro.* T cell-derived cytokines and signals delivered through CD40 crosslinking induce higher levels of proliferation, IgM secretion, and enhanced expression of costimulatory molecules in NZB/W F1 B cells [37].

B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) play key roles in peripheral B cell survival, maturation, and differentiation. In NZB/W F1 mice, chronic activation of the immune system induced an increase in the levels of circulating BAFF and APRIL. The continuous activation of B cells and thus overexpression of BAFF and APRIL may contribute to an increase in the generation of autoreactive B cells and a thus furthering the development of autoimmune disease [38].

B cells activation by T cells leads to the differentiation of B cells into long-lived plasma cells. However, continuous activation in autoimmune NZB/W F1 mice also generates short-lived plasmablasts. The number of splenic antibody-secreting cells (ASC) increases in NZB/W F1 mice aged 1–5 months and stabilizes after this period. Less than 60% of the splenic auto-ASCs are short-lived plasmablasts, whereas 40% are non-dividing, long-lived plasma cells with a half-life of 6 months. Although anti-proliferative immunosuppressive therapy depleted short-lived plasmablasts, long-lived plasma cells survived and continued to produce autoantibodies [39]. Additionally, Cheng et al. demonstrated that autoantibodies from long-lived "memory" plasma cells of NZB/W F1 mice drive complex immune nephritis [40].

5. Genetic characteristics: susceptibility loci in NZB and NZW mice and in the NZB/W F1 hybrid

Several chromosomal regions containing genes affecting lupus susceptibility or resistance have been identified pointing that murine lupus is genetically complex and mediated by a combination of genes.

In NZB/W F1 hybrids, genetic interactions between alleles present in NZB and NZW are the causes of the severe systemic autoimmunity found in these mice, due to the generation of a phenotype that is absent in both parental strains.

To search for contributing loci in this model of SLE, investigators backcrossed NZB/W F1 mice to NZW, then used brother-sister mattings to generate 27 substrains, termed New Zealand mixed (NZM) mice [41]. Further analysis of these 27 substrains led to the selection of NZM2410 as a lupus model. Susceptibility to lupus in NZM2410 is predominantly due to genes localized to the telomeric region of chromosome 1 (Sle1), the middle of chromosome 4 (Sle2), and the centromeric segment of chromosome 7 (Sle3) [42]. To study the contribution of each of these loci to pathogenesis, congenic strain construction was performed by transferring each of these intervals from NZM2410 onto the B6 background. Phenotypic analysis of congenic mice revealed that each locus contributes a unique component phenotype to the disease [43]. Although the B6.Sle congenic strains express phenotypes relevant to autoimmunity, none develop severe pathology, indicating that individual genes are not sufficient to cause lupus. The co-expression of these three major loci is necessary and sufficient for the development of a fully penetrant disease. These studies demonstrated that susceptibility to lupus involves both genetic interactions and additive effects of individual genes.

Additionally, to the Sle susceptibility loci, other loci present on chromosomes 1, 4, 7, and 17 have been associated with susceptibility in multiple lupus-prone strains including the NZB/W F1 model, an indication that genes in these regions may be necessary for immune regulation and function.

5.1 Susceptibility loci for systemic lupus on chromosome 1: Sle1, Nba2, Lbw7, Sbw1, and Cgnz1

The congenic strain, B6.Sle1, develops autoantibodies against nuclear autoantigens and displays spontaneous T cell activation without developing

glomerulonephritis [44]. Fine mapping of the Sle1 locus determined that four loci within this congenic interval, termed Sle1a, Sle1b, Sle1c, and Sle1d, are implicated in the loss of tolerance to chromatin [45, 46].

Analyses of NZB congenic mice, (NZB X SM/J)F1 X NZB, revealed that the Nba2 lupus susceptibility locus is associated with hypergammaglobulinemia and the development of various autoantibodies, including anti-DNA, anti-chromatin, and anti-gp70 [47]. In these studies, mice congenic for the Nba2 locus did not develop significant renal disease on a B6 background but developed severe lupus nephritis when crossed with NZW mice [48], consistent with the need of multiple susceptibility genes for full expression of lupus.

The susceptibility loci, Sle1 and Nba2, overlap in the same region of chromosome 1, suggesting that some susceptibility genes may be shared among lupus-prone strains. Within The Nba2 and Sle1 genetic segment there are genes encoding for the inhibitor type IIFcγR (FcγR IIB) [49], members of the SLAM/CD2 family of immunomodulatory receptors (Cd244, Cd229, Cs1, Cd48, Cd150, Ly108, and Cd84) [45] and members of the IFN-inducible (Ifi) family [48] all of which can regulate cell proliferation and survival. Analysis of congenic strains demonstrated that the presence of nuclear antigens and the severity of renal disease are linked with the FcγR and SLAM gene clusters with little involvement from the Ifi interval [50].

The inhibitory receptor for IgG, FcγRIIB, appears to be a fundamental regulator of B cell as well as myeloid cell activation [51]. Deficiencies in these routes result in heightened humoral and inflammatory responses, further contributing to lupus pathology [52].

The complement receptor 2 (CR2) gene, which encodes the complement receptor type 2 that acts as a B cell co-receptor is also in the Sle1c interval [53].

Theofilopoulos and colleagues identified Sbw1 and Lbw7 in chromosome 1 during their original linkage analysis of (NZB X NZW) F2 progeny [54]. Sbw1 defines a locus associated with splenomegaly, while Lbw7 defines a locus associated with anti-chromatin autoantibodies. Lbw7 of NZW origin is likely to be identical to Nba2 from NZB [54]. Additionally, Cgnz1 was detected in lupus-prone NZM2338 mice and significantly linked to chronic glomerulonephritis, severe proteinuria, and early mortality in female mice [55].

5.2 Susceptibility loci for systemic lupus on chromosome 4: Sle2, Nba1, Sgp4, Lbw2, Sbw2, and Adnz1

The congenic strain, B6.Sle2, displays lowered B cell activation thresholds coincident with the appearance of polyclonal IgM in the sera and expansion of the B1a cell compartment, in the absence of glomerulonephritis [43]. Interestingly, combining this locus with Sle1, resulted in glomerulonephritis and enhanced mortality compared with the single congenic strains alone [56].

Another susceptibility locus present on chromosome 4 is the Nba1 locus from NZB and the Lbw2 susceptibility locus from NZB/W F1. Both are associated with kidney disease, while another locus, sbw2, is associated with splenomegaly. The Sbw2 locus mapped to the same region as Lbw2, suggesting a single locus with pleiotropic effects [54]. The Nba1/Lbw2 interval contains the C1qa gene encoding the first component of complement C1q. It has been shown that an insertion polymorphism in the NZB sequence upstream of C1q gene may be related to a limited degree of C1q production, which may confer a risk for lupus nephritis by reducing IC clearance and promoting IC deposition in the glomeruli [57].

Overlapping with the Nba1 locus, there is a locus designated Sgp4, which was linked to the production of nephritogenic gp70 antigens. Production of autoantibodies to the retroviral envelope glycoprotein gp70, and the generation of

gp70-anti-gp70 immune complexes (gp70 IC) have been implicated in the development of nephritis in these lupus models [58, 59].

An additional study using NZM2328 mice found that the NZB-derived locus Adnz1 also contributed to the production of anti-DNA autoantibodies but not to lupus nephritis [55].

5.3 Susceptibility loci for systemic lupus on chromosome 7: Sle3, Lbw5, Nba5, and Aia3

Chromosome 7 contains several susceptibility genes regulating nephritis and autoantibodies. Among them are the Sle3 and Lbw5 loci, both derived from the NZW strain and the Nba5 locus from the NBW strain. A candidate gene present in this region is Cd22, which functions as a negative regulator of BCR signaling transduction.

Sle3 appears to be responsible for the hyperactive and pro-inflammatory antigen-presenting capacity of dendritic cells and macrophages [60].

The Nba5 susceptibility locus was associated with higher titers of anti-gp70 autoantibodies [61], while Aia3 with autoimmune hemolytic autoimmunity in a linkage analysis of NZB [62].

5.4 Susceptibility loci for systemic lupus on chromosome 17: Lbw1 (MHC)

The contribution of MHC haplotype to disease was first reported in the NZB/NZW F1 model [63]. These genes are located in chromosome 17. Several studies demonstrated a strong association of H2d/z heterozygosity with the development of SLE, indicating a co-dominant contribution from each strain, H2d from NZB and H2z from NZW [64].

6. Influence of sex

Differences between female and male responses to foreign and self-antigens have been well-documented. It was suggested that genes and hormones are involved in the differences found in their innate and adaptive immune responses. Generally, females mount higher immune responses than males, which can contribute to the increased susceptibility to autoimmune diseases in females [65].

Similar to humans, within the NZB/W F1 mouse model lupus develops primarily in females with a lesser percentage and severity in male mice. In female mice, lupus signs appear after 6 months of age, with 50% mortality at 8.5 months and 90% mortality at 12.8 months. Male mice develop the disease after a year of age with 50% mortality at about 15 months of age [66]. Accordingly, early studies performed in NZB/W F1 mice showed that estrogen supplementation is associated with a worsening disease and shorter lifespan than untreated littermate. In contrast, supplementation of a female with the male sex hormone 5α-dihydrotestosterone reduce immune complex deposition and prolong survival despite the presence of high levels of IgG antibodies to DNA. Additionally, castrated or 17β-estradiol-treated NZB/W F1 male mice have an earlier onset of lupus and accelerated mortality, suggesting a suppressive effect of androgen [67, 68]. Data accumulated during the past few years provide evidence that female hormones, particularly estrogens, promote lupus pathogenesis. However, some opposite results are suggesting that sexual dichotomy is due to protective effects of androgens. The mortality induced by estrogens may be due to toxic effects rather than accelerated autoimmunity [69].

Cells of the immune system, including B cells, express the cellular receptors for estrogens, estrogen receptor-α (ERα), and estrogen receptor-β [70]. Global disruption of the ERα gene in NZB/W F1 causes a significant reduction in the concentration of anti-histone/DNA and anti-double-stranded DNA IgG antibodies, which are associated with glomerulonephritis. This loss of tolerance was observed in female mice whereas, more modest effects are seen in males [71] suggesting that the ability of ERα signaling to enhance autoantibody production and lupus pathogenesis is more pronounced in females than in males. Additionally, specific deletion of ERα in B cells retards the production of autoantibodies and the development of nephritis in NZB/W F1 mice, demonstrating that ERα acts in a B cell-intrinsic manner to control B cell activation, autoantibody production, and lupus nephritis [72].

B cells with the CD5 marker, which spontaneously produce IgM, are found in higher numbers in NZB mice and have been implicated in lupus [73]. Treatment of lupus-prone female NZB/W F1 mice with tamoxifen (TAM), a synthetic antiestrogen with high affinity for the estrogen receptor, decreases the percentage of B cells and CD5+ B cells in the spleen. Also, TAM-treated mice had less severe proteinuria and increased survival rate compared to controls [74].

On the other hand, it has been described that NZB/W F1 males have higher levels of a population of $Gr1^{high}$Ly-6G + CD11b + myeloid cells that protect them against lupus development [75]. This population is testosterone-regulated and suppresses autoantibody production *in vivo*. Additionally, Gr1+ cells from NZB/W F1 males suppress the differentiation and effector function of CXCR5+ PD-1+ T follicular helper cells, germinal center formation, and plasma cell differentiation [76].

Since sex hormones can bind transcription factors, they might affect autoimmunity via their effects on gene transcription. Accordingly, it has been demonstrated that estrogen upregulates the expression of IFN-γ through the ERα [71].

Additionally, the expression of interferon regulatory factor 5 (IRF5), a lupus susceptibility factor that controls the expression of type I IFNs, is higher in NZB/W F1 females than in males. IRF5 expression also depends on ERα expression, because of splenic cells from ERα knockout female express lower levels of IRF5 [77]. This suggests a (positive) feedback loop between the IFNs and estrogens since activation of type I IFNs or IFN-γ signaling upregulates the expression of ERα [78].

Other studies have provided evidence that lupus-associated miRNAs are differentially expressed in splenocytes of NZB/W F1 male and female mice. Additionally, these miRNAs were upregulated by estrogen treatment [79]. miRNAs regulate the expression, mainly at the post-transcriptional level, of some genes that are important in the development of the innate and adaptive immune system and the maintenance of immune homeostasis. Dysregulation of miRNAs impacts the function of different types of immune cells causing a breakdown of immune tolerance and ultimately the development of autoimmune-related disorders such as SLE [80].

7. Treatment of murine SLE

Different treatments to improve lupus have been evaluated in the NZB/W F1 murine model. In this section, we will review some well-documented procedures.

Interleukin-6 (IL-6) is a multifunctional cytokine synthetized by macrophages, monocytes, and B and T cells. IL-6 is critical for B cell differentiation and maturation, immunoglobulin secretion, cytotoxic T cell differentiation, acute-phase protein production, bone marrow progenitor stimulation, renal mesangial cell

proliferation, and macrophage/monocyte functions. Lupus mice treated with anti-IL-6 mAb reduce B cell proliferation, the ds-DNA antibodies production, and kidney damage [81]. Additionally, treatment with antibodies against the IL-6 receptor (IL6R-mAb) inhibits the production of anti-DNA and anti-TNP IgGs antibodies, and consequently, this treatment increases the survival of the mice [82]. Tocilizumab, an anti-IL6R-mAb commercialized mainly for the treatment of rheumatoid arthritis [83], has been evaluated in SLE patients. This procedure decreases anti-dsDNA antibody levels and circulating plasma cells and improves arthritis and medical scores [84].

Interleukin-10 (IL-10) is a cytokine produced by subsets of activated T cells and macrophages. It mediates a variety of both immunostimulatory and immunosuppressive properties. IL-10 neutralization with anti-IL-10 delays the onset of the disease, increasing survival from 10 to 80% in mice at 9 months. Autoimmunity protection by IL-10 antagonism appeared to be due to an upregulation of endogenous tumor necrosis factor alpha (TNF-α) [85].

TNF-α is a pleiotropic cytokine with immunostimulatory and proinflammatory activities. TNF-α stimulates T and B cell proliferation, immunoglobulin synthesis, enhances natural killer (NK) cell activity, and boosts neutrophil activation. The NZB/W F1 mice have reduced levels of TNF-α, and their treatment with recombinant TNF-α increased their survival [86]. Infliximab, a TNF-α blocking antibody, was evaluated in short- and long-term therapy in SLE patients showing several adverse effects in long-term therapy [87]. Infliximab and Etanercept are another TNF-α blockers commercialized mainly to treat rheumatoid arthritis [88, 89].

Type I interferons (IFN) are primarily regarded as inhibitors of viral replication. However, type I IFN, mainly IFN-α, plays a major role in activation of both the innate and adaptive immune system [90]. IFN-α signature precedes the onset of lupus in NZB/W F1 mice and in humans. Treatment with a vaccine that induces the secretion of anti-IFN-α neutralizing antibodies causes a delay in proteinuria development, low deposits of immune complexes, and increases survival [91]. Two antibodies against IFN-α, Sifalimumab and Rontalizumab, evaluated in SLE patients correlate with improvements in disease activity [92, 93].

BAFF is a B cell-activating factor essential for the survival of B cells. BAFF is produced predominantly by myeloid cells and binds to three distinct receptors on the B cell surface; the transmembrane activator and calcium modulator ligand interactor (TACI), the B cell maturation antigen (BCMA), and the BAFF receptor. Treatment with soluble TACI-Ig fusion protein inhibits the development of proteinuria and prolongs animal survival [94]. Besides, a short course of TACI-Ig and CTLA4-Ig induces a profound depletion of splenic B cells, prolong life, and even reverse proteinuria in aged NZB/W F1 mice [95]. Atacicept is a recombinant fusion protein that blocks activation of B cells by binding to TACI ligands. In SLE patients, the Atacicept treatment favors the reductions in disease activity and severe flares [96].

CD20 is a transmembrane phosphoprotein specifically expressed on B cells. Depletion of B cells with a monoclonal antibody against CD20 favors the survival of aged NZB/W F1 mice [97]. Rituximab, an anti-CD20 monoclonal antibody frequently used in SLE patients improves lupus nephritis, arthritis, serositis, cutaneous vasculitis, mucositis, rashes, fatigue, and neurologic symptoms [98]. Although rituximab's mechanisms of action are not known, its effects are likely mediated by antibody-dependent cell-mediated cytotoxicity and the induction of apoptosis on B cells [99].

Mammalian target of rapamycin (mTOR) is a protein kinase that regulates different cellular processes such as cell proliferation, growth, motility, cell survival,

protein synthesis, and transcription. NZB/W F1 mice treated with rapamycin (a drug used in rejection prophylaxis in solid organ transplantation) from 12 to 37 weeks of age inhibit the production of autoantibodies, development of proteinuria, and prolong mouse survival [100]. Moreover, in mice with established nephritis, rapamycin suppressed the interstitial infiltration of T cells, B cells, and macrophages [101].

Antigen presentation process involves costimulatory molecules CD28, and CTLA4 expressed on T cells, representing activation or inhibitory signals to T cells. CD28 and CTLA4 bind with medium or high affinity, respectively to B7, i.e., expressed on antigen-presenting cells (APCs) [102]. Abatacept is a fusion CTLA4-Ig protein that interrupts the interaction of B7 with CD28. NZB/W F1 mice that express murine CTLA4-Ig exhibit an improvement in all of lupus symptoms increasing survival [103]. In humans, Abatacept is mainly used in rheumatoid arthritis [104], although there are some SLE studies, one of them showing improvement in skin lesions in SLE patient [105].

Based on studies done in mouse models, most clinical trials have focused on agents that control B and T lymphocytes activations and functions. **Figure 1** shows some therapeutic targets investigated in mouse models of SLE (as described in [82, 85, 91, 95, 97, 103, 106–110]), many of which where then follow up in clinical trials [88, 89, 92, 98, 104, 111–118].

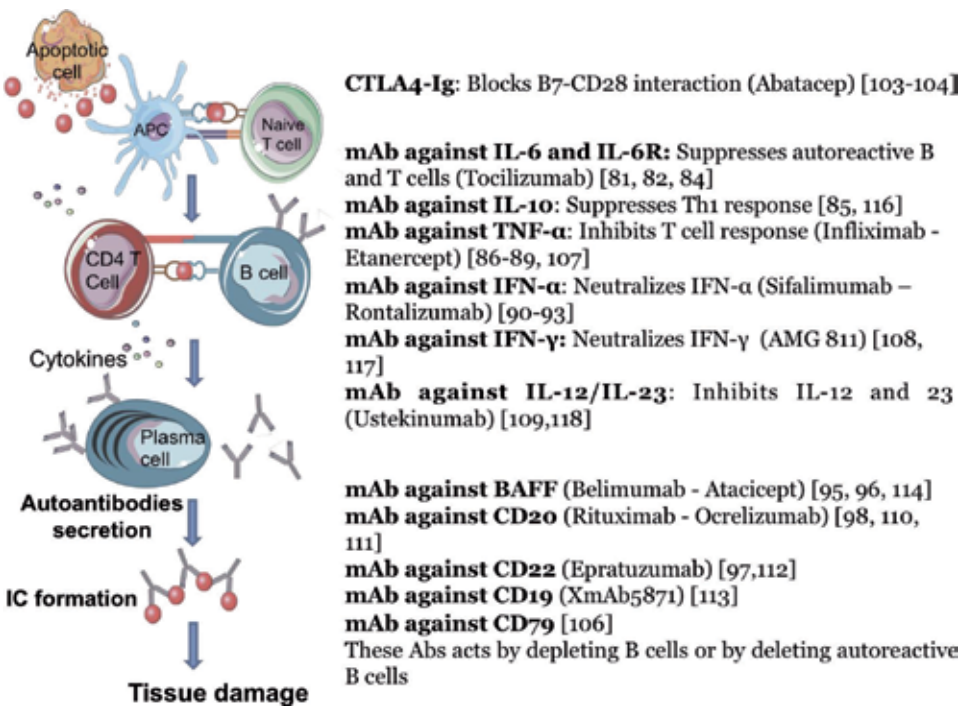


Figure 1.
Immune cells contribution to SLE and potential targets for lupus therapies, as tested in mouse models: Defects in phagocytosis of apoptotic cells leads to the presentation of autoantigens by APC to naive CD4 T cells. Activated T cells help the differentiation of B cell into plasma cells that secrete high levels of autoantibodies. These autoantibodies form immune complexes by binding to autoantigens, and engaging Fcγ receptors on different cell types. This supports inflammation and tissue destruction through the recruitment of inflammatory cells to tissues. APC: Antigen-presenting cell, IC: Immune complexes, mAb: monoclonal antibody. Texts on the right side of the figure show the different targets tested for lupus therapy. Drug names are shown in brackets

8. Conclusions

The spontaneous mouse model of lupus NZB/W F1 has been important to elucidate the pathogenesis of SLE. In this model, the lupus-like phenotypes include lymphadenopathy, splenomegaly, elevated serum antinuclear autoantibodies including anti-dsDNA IgG, and immune complex-mediated glomerulonephritis that are remarkably similar to the pathology described in human lupus. Consequently, it has provided a powerful tool to our knowledge on human lupus disease and the development of novel therapies. Additionally, similar to humans, lupus develops primarily in female NZB/W F1 mice with lesser percentage and severity in male. The female predominance of the disease remains poorly understood; however, hormonal contributions to immune system activation and X chromosome gene-dose effect have been proposed to be the important contributor to sex bias [66]. On the other hand, unlike SLE patients, NZB/W F1 mice do not manifest skin disease or arthritis [3].

Furthermore, human and murine lupus is characterized by a deregulation in autoreactive T helper cells, B and DC cells activation, and cytokine production. Defective function of regulatory T cells, inefficient clearance of immune complex and biological waste, nucleic acid sensing and IFN production pathways are also involved in the loss of tolerance and tissue damage associated to lupus [119]. The use of mouse models has allowed the study of the mechanisms involved in the cellular immune abnormalities, providing a powerful tool to identify novel pathways and targets for disease therapies. Several components of the immune system, such as cytokines, B cells, T cells, and hormones have been identified as potential targets for novel drugs. The side effects, dosage regimens, and response to treatment are first tested on murine models of lupus prior they go to clinical trials. Murine models of disease represent genetically homogeneous populations and in contrast to humans that take chronic doses of immunosuppressant, they allow for examination in the absence of any therap. Despite favorable results in mouse studies, many therapies have failed to meet clinical end points. This is probably because of the complexity of the disease, which involves the contribution of environmental and genetic susceptibility factors [119]. However, some of the therapeutic approaches have been successful recommended for SLE treatment, like Belimumab, a humanized monoclonal antibody directed against B cell activating factor. Additionally, other available agents such as rituximab, tacrolimus, azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil are widely used off-label in SLE [9, 120].

The use of murine models has identified several novel candidate genes, and some of them have been associated to SLE in humans. An important contribution of the genetic studies in NZB/W F1 was the identification, in chromosome 1, of Sle1 and Nba2 loci, which are responsible for the production of autoantibodies. Sle1 and Nba2 encode members of the FcγR, SLAM, and IFN-inducible receptor families.

As sustained above, all the mouse models, and specifically the NZB/W F1, have the benefit of having a shorter evolution of the disease, allowing to investigate the full progression of the disorder and its pathophysiology and to test for possible therapies in a much shorter time period. In spite of their limitations and the fact that one cannot readily extrapolate to the human disease, mouse models of lupus have significantly helped researchers to advance our knowledge on this syndrome, adding relevant data on the pathogenesis of lupus and providing investigators with a valuable preclinical model for the design of future therapies. In spite of the various differences found between the human and mouse immune systems, there are sufficient similarities in the manifestation of the disease to be optimistic regarding

the use of this mouse model to further advance in our understanding of the physiology of the human disease and the formulation of creative new therapies.

Acknowledgements

This work was supported by the Government of Chile through the Programa de Apoyo a Centros Científicos y Tecnológicos de Excelencia con Financiamiento Basal AFB 170004, from the Postdoctoral Fondecyt Project 3160224 and CONICYT doctoral fellowship 21130598.

Conflict of interest

The authors declare no competing or financial interests.

Author details

Gabriela Tejon[1], Yessia Hidalgo[1], Maria Rosa Bono[1] and Mario Rosemblatt[1,2,3]*

1 Department of Biology, Faculty of Sciences, University of Chile, Santiago, Chile

2 Faculty of Life Sciences, Andres Bello University, Santiago, Chile

3 Sciences and Life Foundation, Santiago, Chile

*Address all correspondence to: mrosemblatt@cienciavida.org

References

[1] Hahn BH, Kono DH. 14—Animal models in lupus. In: Wallace DJ, Hahn BHBT-DLE and RS Ninth E, editors. Dubois' Lupus Erythematosus Relat Syndr [Internet]. London: Content Repository Only. 2019. pp. 164-215. Available from: http://www.sciencedirect.com/science/article/pii/B9780323479271000141

[2] Li W, Titov AA, Morel L. An update on lupus animal models. Current Opinion in Rheumatology. 2017;**29**: 434-441. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28537986

[3] Richard ML, Gilkeson G. Mouse models of lupus: What they tell us and what they don't. Lupus Sci Med. 2018;**5**:e000199. Available from: http://lupus.bmj.com/lookup/doi/10.1136/lupus-2016-000199

[4] Mathian A, Weinberg A, Gallegos M, Banchereau J, Koutouzov S. IFN-induces early lethal lupus in preautoimmune (New Zealand Black x New Zealand White)F1 but Not in BALB/c Mice. Journal of Immunology. 2005;**174**: 2499-2506. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.174.5.2499

[5] Liu Z, Bethunaickan R, Huang W, Lodhi U, Solano I, Madaio MP, et al. Interferon-α accelerates murine systemic lupus erythematosus in a T cell-dependent manner. Arthritis and Rheumatism. 2011;**63**:219-229. Available from: http://doi.wiley.com/10.1002/art.30087

[6] Andrews BS. Spontaneous murine lupus-like syndromes. Clinical and immunopathological manifestations in several strains. The Journal of Experimental Medicine. 1978;**148**: 1198-1215. Available from: http://www.jem.org/cgi/doi/10.1084/jem.148.5.1198

[7] Sasaki T, Kadono T, Endo F, Ishida S, Yoshinaga K. Induction of immunological tolerance to single-stranded and double-stranded DNA. Scandinavian Journal of Immunology. 1982;**16**:191-200. DOI: 10.1111/j.1365-3083.1982.tb00714.x

[8] Hirose S, Kinoshita K, Nozawa S, Nishimura H, Shirai T. Effects of major histocompatibility complex on autoimmune disease of H-2-congenic New Zealand mice. International Immunology. 1990;**2**:1091-1095. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2083229

[9] Perry D, Sang A, Yin Y, Zheng Y-Y, Morel L. Murine models of systemic lupus erythematosus. Journal of Biomedicine & Biotechnology. 2011;**2011**:271694. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21403825

[10] Monneaux F, Dumortier H, Steiner G, Briand J-P, Muller S. Murine models of systemic lupus erythematosus: B and T cell responses to spliceosomal ribonucleoproteins in MRL/Faslpr and (NZB × NZW)F1 lupus mice. International Immunology. 2001;**13**:1155-1163. Available from: https://academic.oup.com/intimm/article-lookup/doi/10.1093/intimm/13.9.1155

[11] Brick JE, Ong SH, Bathon JM, Walker SE, O'Sullivan FX, DiBartolomeo AG. Anti-histone antibodies in the serum of autoimmune MRL and NZB/NZW1 F1 mice. Clinical Immunology and Immunopathology. 1990;**54**:372-381. Available from: https://www.ncbi.nlm.nih.gov/pubmed/2302840

[12] Lin BF, Jeng SJ, Chiang BL, Huang CC. Dietary fat affects lipids and anti-cardiolipin antibody levels in autoimmune-prone NZB/W F1 mice. The British Journal of Nutrition. 1997;**77**:657-669. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9155512

[13] Murakami M, Yoshioka H, Shirai T, Tsubata T, Honjo T. Prevention of autoimmune symptoms in autoimmune-prone mice by elimination of B-1 cells. International Immunology. 1995;**7**:877-882. DOI: 10.1093/intimm/7.5.877

[14] Kanno K, Okada T, Abe M, Hirose S, Shirai T. CD5+ B cells as precursors of CD5- IgG anti-DNA antibody-producing B cells in autoimmune-prone NZB/W F1 mice. Annals of the New York Academy of Sciences. 1992;**651**:576-578. Available from: http://www.ncbi.nlm.nih.gov/pubmed/1376080

[15] Helft J, Böttcher J, Chakravarty P, Zelenay S, Huotari J, Schraml BU, et al. GM-CSF mouse bone marrow cultures comprise a heterogeneous population of CD11c+MHCII+ macrophages and dendritic cells. Immunity. 2015;**42**:1197-1211. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1074761315002162

[16] Gleisner MA, Reyes P, Alfaro J, Solanes P, Simon V, Crisostomo N, et al. Dendritic and stromal cells from the spleen of lupic mice present phenotypic and functional abnormalities. Molecular Immunology. 2013;**54**:423-434. DOI: 10.1016/j.molimm.2013.01.011

[17] Zhou Z, Ma J, Xiao C, Han X, Qiu R, Wang Y, et al. Phenotypic and functional alterations of pDCs in lupus-prone mice. Scientific Reports. 2016;**6**:20373. Available from: http://www.nature.com/articles/srep20373

[18] Okamoto A, Fujio K, van Rooijen N, Tsuno NH, Takahashi K, Tsurui H, et al. Splenic phagocytes promote responses to nucleosomes in (NZB x NZW) F1 mice. Journal of Immunology. 2008;**181**:5264-5271. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18832681

[19] Zhan Y, Carrington EM, Ko H-J, Vikstrom IB, Oon S, Zhang J-G, et al. Bcl-2 antagonists kill plasmacytoid dendritic cells from lupus-prone mice and dampen interferon-α production. Arthritis & Rhematology. 2015;**67**:797-808. DOI: 10.1002/art.38966

[20] Potter PK, Cortes-Hernandez J, Quartier P, Botto M, Walport MJ. Lupus-prone mice have an abnormal response to thioglycolate and an impaired clearance of apoptotic cells. Journal of Immunology. 2003;**170**:3223-3232. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.170.6.3223

[21] Licht R, Dieker JWC, Jacobs CWM, Tax WJM, JHM B. Decreased phagocytosis of apoptotic cells in diseased SLE mice. Journal of Autoimmunity. 2004;**22**:139-145. Available from: http://www.ncbi.nlm.nih.gov/pubmed/14987742

[22] Russell PJ, Cameron FH. Studies of macrophage function in murine systemic lupus erythematosus. 4. failure to reverse the defect in fc-mediated phagocytosis and binding by in vitro stimulants or prostaglandins. Pathology. 1986;**18**:59-63. Available from: https://www.sciencedirect.com/science/article/pii/S0031302516368313

[23] Sahu R, Bethunaickan R, Singh S, Davidson A. Structure and function of renal macrophages and dendritic cells from lupus-prone mice. Arthritis & Rheumatology (Hoboken, NJ). 2014;**66**:1596-1607. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24866269

[24] Ogawa Y, Yoshinaga T, Nishikawa M, Takakura Y. Unique cytokine production profile following stimulation with DNA in macrophages from NZB/W F1 mice. Biological & Pharmaceutical Bulletin. 2008;**31**:1244-1249. Available from: http://joi.jlc.jst.go.jp/JST.JSTAGE/bpb/31.1244?from=CrossRef

[25] Alarcón-Riquelme ME, Möller G, Fernández C. Macrophage depletion

decreases IgG anti-DNA in cultures from (NZB x NZW)F1 spleen cells by eliminating the main source of IL-6. Clinical and Experimental Immunology. 1993;**91**:220-225. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1554691&tool=pmcentrez&rendertype=abstract

[26] Enghard P, Langnickel D, Riemekasten G. T cell cytokine imbalance towards production of IFN-γ and IL-10 in NZB/W F1 lupus-prone mice is associated with autoantibody levels and nephritis. Scandinavian Journal of Rheumatology. 2006;**35**:209-216. Available from: http://www.tandfonline.com/doi/full/10.1080/03009740500417791

[27] Singh RR, Hahn BH, Tsao BP, Ebling FM. Evidence for multiple mechanisms of polyclonal T cell activation in murine lupus. The Journal of Clinical Investigation. 1998;**102**:1841-1849. Available from: http://www.jci.org/articles/view/3872

[28] Wofsy D, Chiang NY, Greenspan JS, Ermak TH. Treatment of murine lupus with monoclonal antibody to L3T4. I. Effects on the distribution and function of lymphocyte subsets and on the histopathology of autoimmune disease. Journal of Autoimmunity. 1988;**1**:415-431. Available from: http://linkinghub.elsevier.com/retrieve/pii/0896841188900650

[29] Laurent L, Le Fur A, Le Bloas R, Néel M, Mary C, Moreau A, et al. Prevention of lupus nephritis development in NZB/NZW mice by selective blockade of CD28. European Journal of Immunology. 2017;**47**:1368-1376. Available from: http://doi.wiley.com/10.1002/eji.201746923

[30] Humrich JY, Morbach H, Undeutsch R, Enghard P, Rosenberger S, Weigert O, et al. Homeostatic imbalance of regulatory and effector T cells due to IL-2 deprivation amplifies murine lupus. Proceedings of the National Academy of Sciences. 2010;**107**:204-209. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.0903158107

[31] Lourenço EV, Liu A, Matarese G, La Cava A. Leptin promotes systemic lupus erythematosus by increasing autoantibody production and inhibiting immune regulation. Proceedings of the National Academy of Sciences. 2016;**113**:10637-10642. Available from: http://www.pnas.org/content/113/38/10637.abstract

[32] Iikuni N, Lourenco EV, Hahn BH, La Cava A. Cutting edge: Regulatory T cells directly suppress B cells in systemic lupus erythematosus. Journal of Immunology. 2009;**183**:1518-1522. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.0901163

[33] Hu Y-L, Metz DP, Chung J, Siu G, Zhang M. B7RP-1 blockade ameliorates autoimmunity through regulation of follicular helper T Cells. Journal of Immunology. 2009;**182**:1421-1428. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.182.3.1421

[34] Sitrin J, Suto E, Wuster A, Eastham-Anderson J, Kim JM, Austin CD, et al. The Ox40/Ox40 ligand pathway promotes pathogenic Th cell responses, plasmablast accumulation, and lupus nephritis in NZB/W F1 mice. Journal of Immunology. 2017;**199**:1238-1249. Available from: http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.1700608

[35] Cortini A, Ellinghaus U, Malik TH, Cunninghame Graham DS, Botto M, Vyse TJ. B cell OX40L supports T follicular helper cell development and contributes to SLE pathogenesis. Annals of the Rheumatic Diseases. 2017;**76**:2095-2103. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2017-211499

[36] Karpouzas GA, La Cava A, Ebling FM, Singh RR, Hahn BH. Differences between CD8+ T cells in lupus-prone (NZB × NZW) F1 mice and healthy (BALB/c× NZW) F1 mice may influence autoimmunity in the lupus model. European Journal of Immunology. 2004;**34**:2489-2499. Available from: http://doi.wiley.com/10.1002/eji.200424978

[37] Jongstra-Bilen J, Vukusic B, Boras K, Wither JE. Resting B cells from autoimmune lupus-prone New Zealand Black and (New Zealand Black x New Zealand White)F1 mice are hyper-responsive to T cell-derived stimuli. Journal of Immunology. 1997;**159**: 5810-5820. Available from: http://www.jimmunol.org/content/159/12/5810.abstract

[38] Chu VT, Enghard P, Riemekasten G, Berek C. In vitro and in vivo activation induces BAFF and APRIL expression in B cells. Journal of Immunology. 2007;**179**:5947-5957. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.179.9.5947

[39] Hoyer BF, Moser K, Hauser AE, Peddinghaus A, Voigt C, Eilat D, et al. Short-lived plasmablasts and long-lived plasma cells contribute to chronic humoral autoimmunity in NZB/W mice. The Journal of Experimental Medicine. 2004;**199**:1577-1584. Available from: http://www.jem.org/lookup/doi/10.1084/jem.20040168

[40] Cheng Q, Mumtaz IM, Khodadadi L, Radbruch A, Hoyer BF, Hiepe F. Autoantibodies from long-lived 'memory' plasma cells of NZB/W mice drive immune complex nephritis. Annals of the Rheumatic Diseases. 2013;**72**:2011-2017. Available from: http://ard.bmj.com/content/72/12/2011.abstract

[41] Rudofsky UH, Evans BD, Balaban SL, Mottironi VD, Gabrielsen AE. Differences in expression of lupus nephritis in New Zealand mixed H-2z homozygous inbred strains of mice derived from New Zealand black and New Zealand white mice. Origins and initial characterization. Laboratory Investigation. 1993;**68**:419-426. Available from: http://europepmc.org/abstract/MED/8479150

[42] Morel L, Rudofsky UH, Longmate JA, Schiffenbauer J, Wakeland EK. Polygenic control of susceptibility to murine systemic lupus erythematosus. Immunity. 1994;**1**:219-229. Available from: http://linkinghub.elsevier.com/retrieve/pii/1074761394901007

[43] Morel L, Mohan C, Yu Y, Croker BP, Tian N, Deng A, et al. Functional dissection of systemic lupus erythematosus using congenic mouse strains. Journal of Immunology. 1997;**158**:6019-6028. Available from: http://www.jimmunol.org/content/158/12/6019.abstract

[44] Mohan C, Alas E, Morel L, Yang P, Wakeland EK. Genetic dissection of SLE pathogenesis. Sle1 on murine chromosome 1 leads to a selective loss of tolerance to H2A/H2B/DNA subnucleosomes. The Journal of Clinical Investigation. 1998;**101**:1362-1372. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9502778

[45] Wandstrat AE, Nguyen C, Limaye N, Chan AY, Subramanian S, Tian X-H, et al. Association of extensive polymorphisms in the SLAM/CD2 gene cluster with murine lupus. Immunity. 2004;**21**:769-780. Available from: https://www.sciencedirect.com/science/article/pii/S1074761304003127?via%3Dihub

[46] Morel L, Blenman KR, Croker BP, Wakeland EK. The major murine systemic lupus erythematosus susceptibility locus, Sle1, is a cluster of functionally related genes. Proceedings of the National Academy of Sciences of the United States of America.

2001;**98**:1787-1792. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11172029

[47] Vyse TJ, Rozzo SJ, Drake CG, Izui S, Kotzin BL. Control of multiple autoantibodies linked with a lupus nephritis susceptibility locus in New Zealand black mice. Journal of Immunology. 1997;**158**:5566-5574. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9164982

[48] Rozzo SJ, Allard JD, Choubey D, Vyse TJ, Izui S, Peltz G, et al. Evidence for an interferon-inducible gene, Ifi202, in the susceptibility to systemic lupus. Immunity. 2001;**15**:435-443. Available from: http://www.sciencedirect.com/science/article/pii/S1074761301001960

[49] Pritchard NR, Cutler AJ, Uribe S, Chadban SJ, Morley BJ, Smith KGC. Autoimmune-prone mice share a promoter haplotype associated with reduced expression and function of the Fc receptor FcgammaRII. Current Biology. 2000;**10**:227-230. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10704418

[50] Jørgensen TN, Alfaro J, Enriquez HL, Jiang C, Loo WM, Atencio S, et al. Development of murine lupus involves the combined genetic contribution of the *SLAM* and *FcγR* intervals within the *Nba2* autoimmune susceptibility locus. Journal of Immunology. 2010;**184**:775-786. Available from: http://www.jimmunol.org/content/184/2/775.abstract

[51] Ravetch JV, Bolland S. IgG Fc receptors. Annual Review of Immunology. 2001;**19**:275-290. DOI: 10.1146/annurev.immunol.19.1.275

[52] Xiu Y, Nakamura K, Abe M, Li N, Wen XS, Jiang Y, et al. Transcriptional regulation of Fcgr2b gene by polymorphic promoter region and its contribution to humoral immune responses. Journal of Immunology. 2002;**169**:4340-4346. Available from: http://www.jimmunol.org/content/169/8/4340.abstract

[53] Boackle SA, Holers VM, Chen X, Szakonyi G, Karp DR, Wakeland EK, et al. Cr2, a candidate gene in the murine Sle1c lupus susceptibility locus, encodes a dysfunctional protein. Immunity. 2001;**15**:775-785. Available from: http://www.sciencedirect.com/science/article/pii/S107476130100228X

[54] Kono DH, Burlingame RW, Owens DG, Kuramochi A, Balderas RS, Balomenos D, et al. Lupus susceptibility loci in New Zealand mice. Proceedings of the National Academy of Sciences of the United States of America. 1994;**91**:10168-10172. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7937857

[55] Waters ST, Fu SM, Gaskin F, Deshmukh US, Sung S-SJ, Kannapell CC, et al. NZM2328: A new mouse model of systemic lupus erythematosus with unique genetic susceptibility loci. Clinical Immunology. 2001;**100**:372-383. Available from: http://linkinghub.elsevier.com/retrieve/pii/S152166160195079X

[56] Morel L, Croker BP, Blenman KR, Mohan C, Huang G, Gilkeson G, et al. Genetic reconstitution of systemic lupus erythematosus immunopathology with polycongenic murine strains. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**:6670-6675. Available from: https://www.ncbi.nlm.nih.gov/pubmed/10841565

[57] Miura-Shimura Y, Nakamura K, Ohtsuji M, Tomita H, Jiang Y, Abe M, et al. C1q regulatory region polymorphism down-regulating murine C1q protein levels with linkage to lupus nephritis. Journal of Immunology. 2002;**169**:1334-1339. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.169.3.1334

[58] Rigby RJ, Rozzo SJ, Gill H, Fernandez-Hart T, Morley BJ, Izui S, et al. A novel locus regulates both retroviral glycoprotein 70 and anti-glycoprotein 70 antibody production in New Zealand mice when crossed with BALB/c. Journal of Immunology. 2004;**172**:5078-5085. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.172.8.5078

[59] Tucker RM, Vyse TJ, Rozzo S, Roark CL, Izui S, Kotzin BL. Genetic control of glycoprotein 70 autoantigen production and its influence on immune complex levels and nephritis in murine lupus. Journal of Immunology. 2000;**165**: 1665-1672. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.165.3.1665

[60] Sobel ES, Morel L, Baert R, Mohan C, Schiffenbauer J, Wakeland EK. Genetic dissection of systemic lupus erythematosus pathogenesis: evidence for functional expression of Sle3/5 by non-T cells. Journal of Immunology. 2002;**169**:4025-4032. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12244205

[61] Kikuchi S, Fossati-Jimack L, Moll T, Amano H, Amano E, Ida A, et al. Differential role of three major New Zealand Black-derived loci linked with Yaa-induced murine lupus nephritis. Journal of Immunology. 2005;**174**:1111-1117. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=15634937&retmode=ref&cmd=prlinks%5Cnpapers3://publication/uuid/D47DAAC2-3E2D-4916-B7AA-D1D0A495D0F6

[62] Kikuchi S, Amano H, Amano E, Fossati-Jimack L, Santiago-Raber M-L, Moll T, et al. Identification of 2 major loci linked to autoimmune hemolytic anemia in NZB mice. Blood. 2005;**106**:1323-1329. Available from: https://www.ncbi.nlm.nih.gov/pubmed/15860660

[63] Babcock SK, Appel VB, Schiff M, Palmer E, Kotzin BL. Genetic analysis of the imperfect association of H-2 haplotype with lupus-like autoimmune disease. Proceedings of the National Academy of Sciences. 1989;**86**:7552-7555. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.86.19.7552

[64] Paper S, Hirose S, Ueda G, Noguchi K, Okada T, Sekigawa I, et al. Requirement of H-2 heterozygosity for autoimmunity in (NZB × NZW) F1 hybrid mice. European Journal of Immunology. 1986;**16**:1631-1633. DOI: 10.1002/eji.1830161226

[65] Klein SL, Flanagan KL. Sex differences in immune responses. Nature Reviews. Immunology. 2016;**16**:626-638. DOI: 10.1038/nri.2016.90

[66] Dixon FJ, Andrews BS, Eisenberg RA, Mcconahey PJ, Theofilopoulos AN, Wilson CB. Etiology and pathogenesis of a spontaneous lupus-like syndrome in mice. Arthritis and Rheumatism. 1978;**21**:S64-S67. Available from: http://doi.wiley.com/10.1002/art.1780210909

[67] Roubinian JR. Effect of castration and sex hormone treatment on survival, anti- nucleic acid antibodies, and glomerulonephritis in NZB/NZW F1 mice. The Journal of Experimental Medicine. 1978;**147**:1568-1583. Available from: http://www.jem.org/cgi/doi/10.1084/jem.147.6.1568

[68] Roubinian JR, Talal N, Greenspan JS, Goodman JR, Siiteri PK. Delayed androgen treatment prolongs survival in murine lupus. The Journal of Clinical Investigation. 1979;**63**:902-911. Available from: http://www.jci.org/articles/view/109390

[69] Verheul HAM, Verveld M, Hoefakker S, Schuurs AHWM. Effects of ethinylestradiol on the course of spontaneous autoimmune disease in NZB/W and Nod

mice. Immunopharmacology and Immunotoxicology. 1995;**17**:163-180. DOI: 10.3109/08923979509052727

[70] Smithson G, Medina K, Ponting I, Kincade PW. Estrogen suppresses stromal cell-dependent lymphopoiesis in culture. Journal of Immunology. 1995;**155**:3409-3417. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7561035

[71] Bynoté KK, Hackenberg JM, Korach KS, Lubahn DB, Lane PH, Gould KA. Estrogen receptor-α deficiency attenuates autoimmune disease in (NZB × NZW)F1 mice. Genes and Immunity. 2008;**9**:137-152. Available from: http://www.nature.com/articles/6364458

[72] Tabor DE, Gould KA. Estrogen receptor alpha promotes lupus in (NZB×NZW)F1 mice in a B cell intrinsic manner. Clinical Immunology. 2017;**174**:41-52. Available from: http://www.sciencedirect.com/science/article/pii/S1521661616301607

[73] Suzuki N, Sakane T, Engleman EG. Anti-DNA antibody production by CD5+ and CD5- B cells of patients with systemic lupus erythematosus. The Journal of Clinical Investigation. 1990;**85**:238-247. Available from: http://www.jci.org/articles/view/114418

[74] Wu W-M, Lin B-F, Su Y-C, Suen J-L, Chiang B-L. Tamoxifen decreases renal inflammation and alleviates disease severity in autoimmune NZB/W F1 Mice. Scandinavian Journal of Immunology. 2000;**52**:393-400. Available from: http://doi.wiley.com/10.1046/j.1365-3083.2000.00789.x

[75] Trigunaite A, Khan A, Der E, Song A, Varikuti S, Jørgensen TN. Gr-1 high CD11b+ cells suppress B cell differentiation and lupus-like disease in lupus-prone male mice. Arthritis and Rheumatism. 2013;**65**:2392-2402. Available from: http://doi.wiley.com/10.1002/art.38048

[76] Pieterse E, van der Vlag J. Breaking immunological tolerance in systemic lupus erythematosus. Frontiers in Immunology. 2014;**5**:1-8. Available from: http://journal.frontiersin.org/article/10.3389/fimmu.2014.00164/abstract

[77] Shen H, Panchanathan R, Rajavelu P, Duan X, Gould KA, Choubey D. Gender-dependent expression of murine Irf5 gene: Implications for sex bias in autoimmunity. Journal of Molecular Cell Biology. 2010;**2**:284-290. Available from: https://academic.oup.com/jmcb/article-lookup/doi/10.1093/jmcb/mjq023

[78] Panchanathan R, Shen H, Zhang X, Ho S, Choubey D. Mutually positive regulatory feedback loop between interferons and estrogen receptor-α in Mice: Implications for sex bias in autoimmunity. PLoS One. 2010;**5**:e10868. Available from: https://dx.plos.org/10.1371/journal.pone.0010868

[79] Dai R, McReynolds S, LeRoith T, Heid B, Liang Z, Ahmed S, et al. Biology of Sex Differences. 2013;**4**:19. Available from: http://bsd.biomedcentral.com/articles/10.1186/2042-6410-4-19

[80] Shen N, Liang D, Tang Y, de Vries N, Tak P-P. MicroRNAs—novel regulators of systemic lupus erythematosus pathogenesis. Nature Reviews Rheumatology. 2012;**8**:701-709. DOI: 10.1038/nrrheum.2012.142

[81] Liang B, Gardner DB, Griswold DE, Bugelski PJ, Song XYR. Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus. Immunology. 2006;**119**:296-305. Available from: http://doi.wiley.com/10.1111/j.1365-2567.2006.02433.x

[82] Kiberd BA et al. J Am Soc Nephrol. 1993;**4**:58-61. Available from: http://jasn.asnjournals.org/content/4/1/58.abstract

[83] Scott LJ. Tocilizumab: A Review in Rheumatoid Arthritis. Drugs. 2017;**77**:1865-1879. Available from: http://link.springer.com/10.1007/s40265-017-0829-7

[84] Illei GG, Shirota Y, Yarboro CH, Daruwalla J, Tackey E, Takada K, et al. Tocilizumab in systemic lupus erythematosus: Data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study. Arthritis and Rheumatism. 2010;**62**:542-552. Available from: http://doi.wiley.com/10.1002/art.27221

[85] Ishida H, Muchamuel T, Sakaguchi S, Andrade S, Menon S, Howard M. Continuous administration of anti-interleukin 10 antibodies delays onset of autoimmunity in NZB/W F1 mice. The Journal of Experimental Medicine. 1994;**179**:305-310. DOI: 10.1084/jem.179.1.305

[86] Jacob CO, McDevitt HO. Tumour necrosis factor-α in murine autoimmune "lupus" nephritis. Nature. 1988;**331**:356-358. Available from: http://www.nature.com/articles/331356a0

[87] Aringer M, Houssiau F, Gordon C, Graninger WB, Voll RE, Rath E, et al. Adverse events and efficacy of TNF-blockade with infliximab in patients with systemic lupus erythematosus: long-term follow-up of 13 patients. Rheumatology. 2009;**48**:1451-1454. Available from: https://academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/kep270

[88] Nozaki Y, Nagare Y, Ashida C, Tomita D, Okada A, Inoue A, et al. Infliximab dose adjustment can improve the clinical and radiographic outcomes of rheumatoid arthritis patients: REVIVE study results. Biol Targets Ther. 2018;**12**:171-182. Available from: https://www.dovepress.com/infliximab-dose-adjustment-can-improve-the-clinical-and-radiographic-o-peer-reviewed-article-BTT

[89] van Vollenhoven RF, Østergaard M, Leirisalo-Repo M, Uhlig T, Jansson M, Larsson E, et al. Full dose, reduced dose or discontinuation of etanercept in rheumatoid arthritis. Annals of the Rheumatic Diseases. 2016;**75**:52-58. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2014-205726

[90] Rönnblom L, Eloranta M-L, Alm GV. The type I interferon system in systemic lupus erythematosus. Arthritis and Rheumatism. 2006;**54**:408-420. Available from: http://doi.wiley.com/10.1002/art.21571

[91] Zagury D, Le Buanec H, Mathian A, Larcier P, Burnett R, Amoura Z, et al. IFN kinoid vaccine-induced neutralizing antibodies prevent clinical manifestations in a lupus flare murine model. Proceedings of the National Academy of Sciences. 2009;**106**:5294-5299. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.0900615106

[92] Khamashta M, Merrill JT, Werth VP, Furie R, Kalunian K, Illei GG, et al. Sifalimumab, an anti-interferon-α monoclonal antibody, in moderate to severe systemic lupus erythematosus: A randomised, double-blind, placebo-controlled study. Annals of the Rheumatic Diseases. 2016;**75**:1909-1916. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2015-208562

[93] Kalunian KC, Merrill JT, Maciuca R, McBride JM, Townsend MJ, Wei X, et al. A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-α) in patients with systemic lupus erythematosus (ROSE). Annals of the Rheumatic Diseases. 2016;**75**:196-202. Available from: http://ard.bmj.com/lookup/doi/10.1136/annrheumdis-2014-206090

[94] Gross JA, Johnston J, Mudri S, Enselman R, Dillon SR, Madden K, et al. Nature. 2000;**404**:995-999. Available from: http://www.nature.com/articles/35010115

[95] Ramanujam M, Bethunaickan R, Huang W, Tao H, Madaio MP, Davidson A. Selective blockade of BAFF for the prevention and treatment of systemic lupus erythematosus nephritis in NZM2410 mice. Arthritis and Rheumatism. 2010;**62**:1457-1468. DOI: 10.1002/art.27368

[96] Merrill JT, Wallace DJ, Wax S, Kao A, Fraser PA, Chang P, et al. Efficacy and safety of atacicept in patients with systemic lupus erythematosus. Arthritis & Rhematology. 2018;**70**:266-276. Available from: http://doi.wiley.com/10.1002/art.40360

[97] Haas KM, Watanabe R, Matsushita T, Nakashima H, Ishiura N, Okochi H, et al. Protective and pathogenic roles for B cells during systemic autoimmunity in NZB/W F1 Mice. Journal of Immunology. 2010;**184**:4789-4800. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.0902391

[98] Gracia-Tello B, Ezeonyeji A, Isenberg D. The use of rituximab in newly diagnosed patients with systemic lupus erythematosus: long-term steroid saving capacity and clinical effectiveness. Lupus Science & Medicine. 2017;**4**:e000182. Available from: http://lupus.bmj.com/lookup/doi/10.1136/lupus-2016-000182

[99] Thatayatikom A, White AJ. Rituximab: A promising therapy in systemic lupus erythematosus. Autoimmunity Reviews. 2006;**5**:18-24. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1568997205000807

[100] Ramos-Barrón Á, Piñera-Haces C, Gómez-Alamillo C, Santiuste-Torcida I, Ruiz JC, Buelta-Carrillo L, et al. Prevention of murine lupus disease in (NZB×NZW)F1 mice by sirolimus treatment. Lupus. 2007;**16**:775-781. Available from: http://journals.sagepub.com/doi/10.1177/0961203307081401

[101] Lui SL, Tsang R, Chan KW, Zhang F, Tam S, Yung S, et al. Rapamycin attenuates the severity of established nephritis in lupus-prone NZB/W F1 mice. Nephrology, Dialysis, Transplantation. 2008;**23**:2768-2776. Available from: https://academic.oup.com/ndt/article-lookup/doi/10.1093/ndt/gfn216

[102] Sansom DM. CD28, CTLA-4 and their ligands: who does what and to whom? Immunology. 2000;**101**: 169-177. Available from: http://doi.wiley.com/10.1046/j.1365-2567.2000.00121.x

[103] Mihara M, Tan I, Chuzhin Y, Reddy B, Budhai L, Holzer A, et al. CTLA4Ig inhibits T cell–dependent B-cell maturation in murine systemic lupus erythematosus. The Journal of Clinical Investigation. 2000;**106**:91-101. Available from: http://www.jci.org/articles/view/9244

[104] Blair HA, Deeks ED. Abatacept: A review in rheumatoid arthritis. Drugs. 2017;**77**:1221-1233. Available from: http://link.springer.com/10.1007/s40265-017-0775-4

[105] Tarazi M, Aiempanakit K, Werth VP. Subacute cutaneous lupus erythematosus and systemic lupus erythematosus associated with abatacept. JAAD Case Reports. 2018;**4**:698-700. DOI: 10.1016/j.jdcr.2018.03.008

[106] Li Y, Chen F, Putt M, Koo YK, Madaio M, Cambier JC, et al. B cell depletion with Anti-CD79 mAbs ameliorates autoimmune disease in MRL/lpr Mice. Journal of Immunology. 2008;**181**:2961-2972. Available from: http://www.jimmunol.org/content/181/5/2961.abstract

[107] Zhu L-J, Yang X, Yu X-Q. Anti-TNF-alpha therapies in systemic lupus erythematosus. Journal of Biomedicine & Biotechnology. 2010;**2010**:465898. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20625488

[108] Jacob CO, van der Meide PH, McDevitt HO. In vivo treatment of (NZB X NZW)F1 lupus-like nephritis with monoclonal antibody to gamma interferon. The Journal of Experimental Medicine. 1987;**166**:798-803. Available from: http://jem.rupress.org/content/166/3/798.abstract

[109] Kyttaris VC, Kampagianni O, Tsokos GC. Treatment with anti-interleukin 23 antibody ameliorates disease in lupus-prone mice. BioMed Research International. 2013;**2013**:861028. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23841097

[110] Ahuja A, Shupe J, Dunn R, Kashgarian M, Kehry MR, Shlomchik MJ. Depletion of B Cells in murine lupus: Efficacy and resistance. Journal of Immunology. 2007;**179**:3351-3361. Available from: http://www.jimmunol.org/content/179/5/3351.abstract

[111] Mysler EF, Spindler AJ, Guzman R, Bijl M, Jayne D, Furie RA, et al. Efficacy and safety of ocrelizumab in active proliferative lupus nephritis: Results From a randomized, double-blind, Phase III Study. Arthritis and Rheumatism. 2013;**65**:2368-2379. DOI: 10.1002/art.38037

[112] Barry AN, Kilgallen B, Gordon C, Wallace DJ, Isenberg DA, Goldenberg DM, et al. Efficacy and safety of epratuzumab in patients with moderate/severe flaring systemic lupus erythematosus: results from two randomized, double-blind, placebo-controlled, multicentre studies (ALLEVIATE) and follow-up. Rheumatology. 2013;**52**:1313-1322. DOI: 10.1093/rheumatology/ket129

[113] Horton HM, Chu SY, Ortiz EC, Pong E, Cemerski S, Leung IWL, et al. Antibody-mediated coengagement of FcγRIIb and B Cell receptor complex suppresses humoral immunity in systemic lupus erythematosus. Journal of Immunology. 2011;**186**:4223-4233. Available from: http://www.jimmunol.org/content/186/7/4223.abstract

[114] Guerreiro Castro S, Isenberg DA. Belimumab in systemic lupus erythematosus (SLE): Evidence-to-date and clinical usefulness. Therapeutic Advances in Musculoskeletal Disease. 2017;**9**:75-85. Available from: https://www.ncbi.nlm.nih.gov/pubmed/28344669

[115] Wallace DJ, Strand V, Merrill JT, Popa S, Spindler AJ, Eimon A, et al. Efficacy and safety of an interleukin 6 monoclonal antibody for the treatment of systemic lupus erythematosus: A phase II dose-ranging randomised controlled trial. Annals of the Rheumatic Diseases. 2017;**76**:534-542. Available from: http://ard.bmj.com/content/76/3/534.abstract

[116] Llorente L, Richaud-Patin Y, García-Padilla C, Claret E, Jakez-Ocampo J, Cardiel MH, et al. Clinical and biologic effects of anti–interleukin-10 monoclonal antibody administration in systemic lupus erythematosus. Arthritis and Rheumatism. 2000;**43**:1790-1800. DOI: 10.1002/1529-0131(200008)43:8%3C1790::AID-ANR15%3E3.0.CO

[117] Boedigheimer MJ, Martin DA, Amoura Z, Sánchez-Guerrero J, Romero-Diaz J, Kivitz A, et al. Safety, pharmacokinetics and pharmacodynamics of AMG 811, an anti-interferon-γ monoclonal antibody, in SLE subjects without or with lupus nephritis. Lupus Science & Medicine. 2017;**4**:e000226. Available from: http://lupus.bmj.com/content/4/1/e000226.abstract

[118] van Vollenhoven RF, Hahn BH, Tsokos GC, Wagner CL, Lipsky P, Touma Z, et al. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. Lancet. 2018;**392**:1330-1339. DOI: 10.1016/S0140-6736(18)32167-6

[119] Tsokos GC, Lo MS, Reis PC, Sullivan KE. New insights into the immunopathogenesis of systemic lupus erythematosus. Nature Reviews Rheumatology. 2016;**12**:716-730. DOI: 10.1038/nrrheum.2016.186

[120] Wallace DJ. The evolution of drug discovery in systemic lupus erythematosus. Nature Reviews Rheumatology. 2015;**11**:616. DOI: 10.1038/nrrheum.2015.86

Section 2

Reproductive Medicine in Lupus Patients

Chapter 4

Reproductive Environment in Patients with SLE

María del Carmen Zamora-Medina and Juanita Romero-Díaz

Abstract

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disorder that predominantly affects women in reproductive years. Immunologic and hormonal adaptations during pregnancy focused on creating an ideal environment to achieve a successful pregnancy represent a challenge in SLE women as they can influence on disease activity and outcomes during pregnancy. Several disease-related factors such as the presence of antiphospholipid antibodies and anti-SSA/Ro can also impact in the risk of pregnancy adverse outcomes and neonatal complications. Lupus nephritis and preeclampsia share clinical and laboratory features hindering differentiation between both entities. Contraception constitutes a relevant topic in SLE patients to prevent unplanned pregnancies during periods of disease activity or potentially teratogenic drug exposure, but its potential risk on disease flares and thrombotic events is the main concern. Finally, fertility in patients with SLE can be affected by the use of drugs related to infertility that lead to premature ovarian failure. Recently, assisted reproduction technologies have emerged as a safe option in patients with SLE.

Keywords: systemic lupus erythematosus, pregnancy, pregnancy adverse outcomes, neonatal lupus, contraception, antiphospholipid antibodies, anti-SSA/Ro

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease, with a remitting and relapsing course. It mainly affects young women of reproductive age, so addressing issues such as pregnancy, fertility, and reproductive aspects is an essential part of the comprehensive management of these patients.

In the last decades, diagnostic and therapeutic strategies for SLE and consequently the management of pregnancy have improved. Despite these advances, pregnancies in SLE patients are still considered a high-risk condition due to an increased risk of major obstetrical and neonatal complications.

Pregnancy represents a critical period in women's life due to profound immunological and hormonal changes that mostly occur to tolerate the fetus. The interaction of SLE and immunologic adaptations of pregnancy lead to unique challenges in this setting, as alterations in immune mechanisms can have consequences both for the fetus, including a risk of miscarriage or neonatal lupus, and for the mother, including disease flare.

A close relationship between pregnancy and disease flares has been established. The association of SLE and pregnancy, mainly with active disease and lupus nephritis, has poorer outcomes, with increased frequency of preeclampsia (PE), fetal loss,

preterm birth, and intrauterine growth restriction. On the other hand, pregnancy impacts on maternal disease and can be associated with disease flares requiring immunosuppressive therapy.

This chapter will address the immunological and hormonal adaptations during normal pregnancy and the differences between healthy pregnant women and women with SLE. Later, we will focus on the relationship between lupus activity and pregnancy and the impact of SLE on pregnancy outcomes.

2. Interaction between pregnancy and systemic lupus erythematosus

2.1 Immunologic and neuroendocrine environment in pregnancy

Pregnancy represents a major immunological challenge for the maternal body due to fetal expression of paternal antigens. The maternal immune system has to balance the opposing needs of maintaining robust immune reactivity to protect both the mother and the fetus from invading pathogens while at the same time tolerating highly immunogenic paternal alloantigens to sustain fetal integrity [1].

In order to protect the fetus from an attack of the maternal immune system, pregnancy induces profound immune and neuroendocrine changes in the maternal body [2]. Modulation of the function and composition of the different cellular components and immunomodulatory molecules occur during pregnancy in the mother. Also, immune tolerance to paternal antigens is promoted by migration of fetal cells and cell-free DNA to the maternal circulation during pregnancy, which can remain with the mother for decades [3].

During pregnancy, a shift of cytokine profile toward a T-helper 2 (Th2) response instead of Th1 was considered one of the most important immunological modifications. Suppression of Th CD4+ cells (Th1 response) in uncomplicated human pregnancy and Th1 polarization in patients with reproductive failure has supported the concept of successful pregnancy as a Th2 phenomenon proposed by Wegmann [4]. However, recent extensive research on the physiology of pregnancy has shown that the hypothesis that pregnancy is warranted by Th1/Th2 shift is simplistic [5].

During the different stages of pregnancy, cytokine production at the feto-maternal interface is regulated to create optimal conditions for fetal development. Interferon (IFN)-γ and TNF-α, both cytokines secreted by Th1 cells and major contributors to Th1 immune response, are necessary during early stages of pregnancy for successful implantation and placenta development but later in pregnancy could be detrimental and result in pregnancy loss [2]. Chorionic villous tissue expresses not only Th2-type cytokines but also IL-1 β and TNF-α in the first trimester [6]. On the other hand, high expression of IL-10, a pleiotropic cytokine with both immune stimulatory and immune suppressive functions, is present in the human placenta at term [7].

In line with local cytokine modulation and as a reflection of systemic effects of pregnancy, cytokine secretion in peripheral blood mononuclear cells (PBMC) changes during pregnancy. In vitro assays from whole blood of healthy pregnant women have shown a diminished pro-inflammatory response, with a decrease of TNF-α, IL-1β, and IL-6, while IL-4 and IL-10 remain stable during pregnancy [8]. During the third trimester, a reduction of IL-12 and TNF-α production was detected in monocytes from healthy pregnant women compared to postpartum values [9]. An increase of IL-4-secreting PBMC, but not of IFN-γ-positive cells, was found in the second and third trimesters of pregnancy in healthy women after stimulation with paternal antigens [10]. The same group found significantly higher numbers of IFN-γ- and IL-4-secreting

PBMC in all three trimesters of pregnancy and also postpartum than the nonpregnant controls, indicating a systemic upregulation of both Th1- and Th2-like immune responses during normal pregnancy [11].

Besides cytokines, regulatory molecules that modify cytokine actions such as IL-1Ra and IL-6R have been found to be increased in serum of pregnant women, as well as levels of IL-6 and IL-1. Likewise, levels of soluble TNFR were found significantly increased in the second and third trimesters of pregnancy compared to nonpregnant values [3]. Thereby, both Th1- and Th2-type cytokines are important players of immune adaptation to pregnancy at local and systemic levels. Its production is adjusted to the different stages of pregnancy and, in addition with upregulation of cytokine-regulating molecules, can exert an ideal environment to achieve a successful pregnancy.

Pregnancy also induces substantial changes in hormone levels, which have powerful effects on blood cells as they can regulate their proliferation, distribution, and function. Estrogens enhance antibody production, Th2-type immune responses, and B-cell immunity [7]. At high concentrations, such as those found in pregnancy, estrogens and gestagens stimulate the secretion of IL-4, IL-10, TGF-β, and IFN-γ while simultaneously suppressing production of TNF-α [3, 12].

Therefore, pregnancy influences the interaction between neuroendocrine and immune systems both locally and systemically with a fine balance that creates optimal, but not uniform conditions at the feto-maternal interface and in the maternal circulation.

2.2 Maternal tolerance to the fetus in normal pregnancy

Although localized mechanisms at the maternal-fetal interface contribute to fetal evasion from an immune attack, several additional mechanisms operate during pregnancy and help the fetus to evade maternal immune response.

In this context, regulatory T (Treg) cells have been shown to play a pivotal role in maternal-fetal tolerance. These Treg cells, a subset of suppressor CD4+ CD25+ cells, play a dominant role in the maintenance of immunological self-tolerance by preventing immune and autoimmune responses against self-antigens. In recent years, it has been observed that Treg cells are essential in promoting fetal survival, avoiding the recognition of paternal semi-allogeneic tissues by maternal immune system, a critical step for successful pregnancy [13, 14].

In healthy pregnant women, CD4+ CD25+ Treg increases rapidly in peripheral blood peaking at midgestation coinciding with the time of maximal trophoblast invasion and decreasing after delivery to prepregnancy levels [15]. Levels of Treg cells within the decidua, which represents the maternal-fetal interface, are elevated compared with those in the peripheral blood. The increase in Treg cells emphasizes the potential role for these cells in the successful development of the placenta by ensuring fetal tolerance [16].

Expansion of Treg cells is not only due to hormonal changes occurring during pregnancy, but can be driven by several other factors like decidual peptides, fetal antigens, and seminal fluid. Indeed, Treg cells act in an antigen-specific manner as they are specifically activated by MHC paternal antigens, but once activated they are able to exert suppressive effects on other local cells in an antigen-independent manner [16, 17].

The exact mechanism by which Treg cells exert their suppressive activity during pregnancy is not completely clear but is likely to be mediated by cell contact-dependent and cell contact-independent manipulations of dendritic cells (DCs) and effector Th cells, as well as direct cytolytic activity on DCs and modulation of the local metabolic environment [1, 17]. Recent data support the capacity of Tregs to block maternal effector T cells, thereby reducing the maternal-fetal pathological responses to paternal antigens [18].

A prospective observational study of 101 women who underwent in vitro fertilization (IVF) showed an increased level of circulating Treg cells in pregnant women. A higher percentage of Treg in peripheral blood was associated with increased rates of pregnancy and live birth [19]. On the other hand, deficit in Treg cell number in the decidua and maternal peripheral blood has been associated with complications such as unexplained infertility, miscarriage, and preeclampsia [1, 13]. These observations support the Need for a substantial increase in Treg cell numbers for a successful pregnancy.

Interestingly, during pregnancy a bidirectional exchange of cells at the maternal-fetal interface occurs, so maternal cells can cross the placenta and engraft in fetal lymph nodes in utero, a phenomenon called maternal microchimerism. Human fetal T cells are responsive against maternal alloantigen, but a pool of fetal Treg cells actively suppresses their function. Maternal microchimerism has been shown to induce development in utero of fetal Treg cells that suppress fetal antimaternal immune response, indicating a mechanism that promotes tolerance toward maternal antigens by the fetus [14, 20].

Besides Th1 and Th2 cells, there is a third subset of CD4+ T-helper cells called Th17 cells, which, like Treg cells, are implicated in pregnancy and maternal immune tolerance to the fetus [14]. These Th17 cells are defined by their ability to produce IL-17, a pro-inflammatory cytokine that promotes development of Th17 cells and interestingly, in the presence of a tolerance milieu, drives differentiation to Treg cells [21]. Both Treg and Th17 cells require transforming growth factor beta (TGF-β) for differentiation, but the copresence of IL-6 favors differentiation of pathogenic Th17 cells as it can inhibit the generation of FoxP3+ in Treg cells induced by TGF-β [22]. Th17 cells promote inflammation and generally have opposing actions to Treg cells so a reciprocal relationship between these two subsets of Th cells has been described [21].

The presence of Th17 cells in human decidua of healthy pregnancies was investigated. The first-trimester human decidua displayed a local expansion of Treg cells, while a low occurrence of Th17 cells was observed, which suggests that the inverse relationship between Treg and Th17 cells seems to be maintained at least in early stages of pregnancy [23].

On the other hand, increased numbers of Th17 have been found in obstetric complications such as preeclampsia and recurrent pregnancy loss (RPL). A significant increase of Treg FoxP3+ to IL-17-expressing CD4+ T cell ratio in peripheral blood at the third trimester of healthy pregnancy was reported, while an absence of a reduction of IL-17 production toward a FoxP3+ expression was observed in preeclamptic pregnancies [24]. In line with these observations, a later study reported an increased prevalence of IL-17-producing circulating T CD4+ and CD8+ cells in preeclampsia, demonstrating a shift in the Th17/Treg balance in this pregnancy complication [25].

Also, the proportion of Th17 cells in peripheral blood and decidua was significantly higher in unexplained RPL patients compared to normal pregnant women. As reported in preeclamptic pregnancies, there was an inverse relationship between Th17 cells and Treg cells in peripheral blood and decidua in unexplained RSA [26]. Another study showed an accumulation of IL-17-producing cells in decidua of inevitable abortion cases compared to normal pregnancies and missed abortions [27]. Therefore, there is evidence suggesting that balance between Th17 cells and Treg cells may be critical to pregnancy outcomes.

2.3 SLE pregnancy vs. normal pregnancy

Differences in sex steroid hormones during pregnancy have been observed in patients with SLE compared to healthy women. In a prospective study, pregnant

lupus patients presented lower levels of estradiol and progesterone in the second and most of the third trimester of pregnancy [28]. The inability to produce high concentrations of these sex hormones during the last two trimesters of pregnancy could be due to placental insufficiency, which in turn can be implicated with the elevated rate of fetal loss in SLE patients [29].

Levels of certain cytokines involved in the humoral immune response have been shown to be modified in the peripheral circulation of pregnant SLE patients. Serum levels of IL-6, a cytokine necessary for T cell help for B cells and proliferation of plasma cells, are lower than expected in the third trimester of gestation. Higher levels of IL-10 before conception through pregnancy and postpartum in lupus patients compared to healthy controls have been observed, suggesting a constitutional overproduction of IL-10 in SLE patients resulting in a continuous B-cell stimulation. Furthermore, levels of soluble TNF receptor I (sTNFR I) and IL-10 are significantly higher during pregnancy and postpartum in pregnant patients with active SLE compared to healthy controls [28].

Cytokine profile of PBMC in SLE and rheumatoid arthritis (RA) pregnant women was investigated in a prospective study by assessing cytokine messenger RNA (mRNA) expression using quantitative PCR. TNF-α was the most abundant cytokine mRNA expressed in PBMC in all three groups studied (healthy pregnant women, RA, and SLE pregnant patients). However, in RA and SLE patients, a general Th2 response reflected by high IL-10 levels was found [30].

Several studies have investigated the phenotype and function of Treg cells in patients with SLE. Most of the studies have shown a decrease in Treg cell numbers in SLE patients and a negative correlation with disease activity [16, 31–33]. In addition to the reduced number of Treg cells, some data suggest an impaired function of Treg in SLE like a reduced migratory ability [34]. Also, a defect in T-cell suppression has been observed in SLE, although this defect seems to be due to effector cell resistance rather than a reduced Treg suppressor capacity [35].

A pilot study have shown that circulating CD4+ CD25+ FOXP3 Treg cell numbers are markedly reduced in nonpregnant women with SLE compared with healthy controls. Treg levels remained depleted in SLE patients when pregnant, while those in healthy individuals raised, peaking at 10–12 weeks of gestation. Lower quantity of Treg cells was evident regardless of disease activity and medication in SLE patients [21]. So, considering the essential role of Treg cells at early stages of pregnancy and its implication for immune tolerance, defective functioning and decreased number of Treg cells could predispose women with SLE to pregnancy complications.

There is little work investigating the presence of Th17 cells in pregnant SLE patients, although a study supports an imbalance between Treg and numbers of Th17 cells in active SLE. An inverse correlation between Treg/Th17 ratio with severity of active SLE and anti-DNA antibody levels was reported [36]. Disease flares and severe complications of SLE, such a lupus nephritis, seem to be associated with a decrease in FoxP3+ Treg cells and an increase in Th17 cells [37, 38]. In a longitudinal study that evaluated the changes of serum IL-17 and other cytokines in SLE pregnant woman during pregnancy, serum IL-17 concentrations were higher in SLE than in controls with no changes during pregnancy [36].

As discussed previously, TGF-β is essential for the differentiation of both Treg cells and Th17 cells. In a large cohort study, reduced levels of TGF-β were associated with increased SLE activity [39]. Although TGF-β influence in reproduction and complications in pregnancy is not clear, a possible role in trophoblast invasion has been proposed as low levels of TGF-β in the second trimester of pregnant woman have been associated with an increased risk of developing preeclampsia [16]. Clearly, more studies are needed to understand the role of Treg/Th17 imbalance

in SLE pregnancies and its possible implications in the risk of maternal-fetal complications.

As mentioned above, pregnancy induces important hormonal changes. Prolactin (PRL) levels increase progressively during pregnancy and lactation in order to stimulate the synthesis of milk in the mammary glands [42]. Elevated levels of PRL have been found in almost one third of SLE patients, and higher levels during the second and third trimesters have been associated with clinical activity and poor maternal and fetal outcome [40, 41]. On the other hand, the presence of anti-PRL autoantibodies in 13.1% of pregnant patients with SLE has been reported. Likewise, a lower frequency of maternal and fetal complications in SLE patients than those without these antibodies was reported [41].

Therapeutic blockade of PRL with bromocriptine (BRC), a dopamine analog that suppresses PRL secretion, has been evaluated to prevent lupus relapses during pregnancy and postpartum. A pilot study explored the use of BRC between 25 and 35 weeks of gestation in two groups of ten pregnant SLE patients each. No patient in BRC group had disease flares, and there were lower adverse maternal and fetal outcomes in the treatment group than the group that did not receive BRC during pregnancy [42]. More recently, a randomized clinical trial evaluated the use of BRC in the postpartum of 76 SLE pregnant women. BRC administration for 2 weeks after delivery reduced the disease relapse rate of the treatment group [43].

So, results from clinical studies support the contribution of PRL to complications in pregnant SLE women and a possible role of BRC in the prevention of disease relapses during pregnancy and postpartum.

3. Influence of pregnancy in SLE outcomes

The critical immunologic adaptations during pregnancy and postpartum can impact maternal autoimmune diseases in several ways. One is triggering the onset of an autoimmune disease in postpartum or influencing disease activity of an established disease. In this manner, disease response to complex pregnancy changes depends on its pathophysiology [2].

As seen before, steroid hormones and cytokine profiles differ in SLE patients compared with healthy women during pregnancy leading to a dysregulation of the balance between cell-mediated and humoral immune responses, which could explain the variability of the SLE course during gestation [44]. Since SLE is considered mainly a Th2-mediated disease, pregnancy-related changes could trigger disease onset or increase the risk of disease exacerbations during this period [45]. Also, hormones such as estrogen and prolactin could play a role in amplifying the inflammatory effect that characterizes lupus relapses. In murine models, increasing doses of estrogen, like those seen in pregnancy, promotes physiological and immunological changes associated with increased lupus activity [46].

3.1 Lupus activity and its relationship with pregnancy

Whether SLE activity increases during pregnancy or not has been previously debated in the literature. The majority of prospective studies in SLE pregnancies have shown that the risk of disease flare is higher during pregnancy, although some discrepancies exist due to heterogeneity of lupus flare definition and tools used to assess lupus activity [2]. Newer studies using validated instruments for disease activity assessment have found a two–threefold increase in SLE activity during pregnancy [47, 48]. Even though SLE flares occur at any time during pregnancy,

most of these flares are considered mild to moderate in severity and may include renal, hematological, and musculoskeletal systems. Likewise, previous organ involvement predicts the same type of condition during pregnancy, particularly in the case of renal, hematological, and cutaneous activity [36].

Disease activity at conception and in the previous 6 months, both clinical and serological, is a key predictor not only for obstetrical complications but also of SLE flares during pregnancy. Prospective studies of pregnant lupus patients have reported some risk factors for SLE activity during pregnancy: a high number of relapses prior to pregnancy, high SLEDAI index before pregnancy, and preconception SLE activity [46, 49]. In fact, the risk of severe lupus flare is increased about seven times in patients with active SLE at conception [50]. Moreover, SLE disease activity immediately prior to pregnancy also impacts on damage accrual after pregnancy [51].

Besides disease activity at and before conception, several predictors for flares in pregnant patients have been described. A prospective evaluation of 254 patients found that discontinuation of hydroxychloroquine (HCQ) was associated with a higher degree of lupus activity (measured by SLEDAI) during pregnancy as well as an increased rate of flare during this period. On the contrary, women who continued taking HCQ required lower average dose of prednisone during pregnancy [52].

In addition, primigravity seems to influence the risk of lupus flares during pregnancy. A retrospective analysis of 124 pregnancies found that the first pregnancy in SLE women was associated with an increased risk of relapse at any level, particularly in the kidney [53].

On the other side, SLE activity during or prior to pregnancy is associated with several maternal and fetal complications such as fetal loss, preterm birth, intrauterine growth retardation (IUGR), and hypertensive complications. Previous renal disease is also a risk factor for obstetric complications like PE, fetal loss, IUGR, and premature birth. Therefore, early identification and prompt treatment in pregnant women with lupus activity are essential to improve pregnancy outcomes [49]. However, recognition and management of disease flares during pregnancy can be challenging due to the physiological changes that occur during this period, which can overlap with clinical and laboratory features of active SLE [46]. For this reason, clinical data and laboratory findings in pregnant patients with SLE should be interpreted with caution. Thrombocytopenia, mild anemia, and increased erythrocyte sedimentation rate (ESR) often occur during normal pregnancy. In addition, complement levels are less reliable to identify or support the suspicion of disease activity due to its physiological increase during pregnancy, although a decrease in C3 and C4 titers as well as an increase in anti-DNA antibodies may be useful to differentiate complications such as preeclampsia and SLE activity.

3.2 Lupus nephritis, pregnancy, and hypertensive complications

Lupus nephritis is among the findings that most often induces increased morbidity and mortality during pregnancy. Indeed, lupus nephritis, especially active at the time of conception, has been associated with an increased risk of relapse during pregnancy. A higher risk of SLE activity has been reported, particularly renal flares, in pregnant patients with previous nephritis compared to those patients without history of renal involvement [54]. However, a recent prospective multicenter study did not find an increased risk of renal flares during pregnancy in patients with a history of previous renal activity and clinically active lupus nephritis at conception. Instead, history of renal flares before pregnancy predicted hypertensive

Features	Preeclampsia	Lupus nephritis
Timing in pregnancy	>20 weeks of gestation	Throughout gestation and postpartum
Physical findings		
- Hypertension (BP >140/90)	Present	Present
- Edema	Present	Present
- RUQ tenderness	May be present	Absent
- Visual symptoms/seizures	Present with severe features	Absent
Lupus activity		
- Fever	Absent	Present/absent
- Malar rash	Absent	Present/absent
- Arthralgias/arthritis	Absent	Present/absent
- Oral ulcers	Absent	Present/absent
Laboratory findings		
- Proteinuria	Present >20 weeks	Present <20 weeks
- Active urinary sediment	Absent	Present
- Increased creatinine	Usually normal	May be increased
- Complement	Normal/increased	Normal/decreased
- Anti-dsDNA	Absent	May be increased
- aPL antibodies	Absent	May be present
- Abnormal LFTs	Present with severe features	Absent
Renal biopsy findings	Endothelial cell swelling, loss of fenestrations, occluded capillary lumen, rare thrombi	WHO class II to class VI lupus nephritis Thrombi and vascular changes with aPL

Data from [60, 61]. BP, blood pressure; RUQ, right upper quadrant; anti-dsDNA, anti-double-stranded DNA; aPL, antiphospholipids; LFTs, liver function tests

Table 1.
Clinical, laboratory, and renal biopsy findings in preeclampsia and lupus nephritis during pregnancy.

complications such as preeclampsia (PE) [55]. A meta-analysis of 37 studies reported lupus nephritis flare in 16% of pregnant lupus patients and confirmed the association of lupus nephritis at conception with an increased risk of hypertension during gestation. Adverse outcomes in pregnant patients with lupus nephritis were also related to hypertension and presence of antiphospholipid antibodies [56]. Moreover, the onset of PE seems to occur at earlier weeks of gestation in lupus nephritis patients compared to SLE patients without renal involvement [57].

Preeclampsia is a syndrome unique to pregnancy that manifests with hypertension and proteinuria and resolves following delivery. Besides classical risk factors in general population, diseases that promote endothelial dysfunction including SLE increase the risk of preeclampsia. Among lupus pregnancy cohorts, the rate of preeclampsia ranges varies widely. Whereas a meta-analysis of lupus pregnancies reports a preeclampsia rate of 7.8%, other studies suggest that it can be twice as high, particularly in women with nephritis [29, 56]. Dysfunctional angiogenesis leading to an impair in placental development has been implicated in pathogenesis of preeclampsia. Several markers in maternal serum like VEGF, placental growth factor (PlGF), and soluble fms-like tyrosine kinase (sFlt-1) have been found to be predictive of preeclampsia in lupus patients. Lower than expected levels of

proangiogenic factors VEGF and PlGF and high levels of antiangiogenic factor sFlt-1 seem to reflect poor placental perfusion and impaired angiogenesis in the rapidly growing placenta [29].

Similar to what happens in lupus flares during pregnancy, distinguish clinical indicators of lupus nephritis from pregnancy physiological features, and those related preeclampsia can be a complex task. In the first trimester of pregnancy, maternal systemic circulation suffers remarkable physiological vasodilation conditioned by relaxin, a hormone produced by the corpus luteum. As a result of systemic vasodilation, glomerular filtration rate (GFR) elevates, and serum creatinine consequently diminishes making it more difficult to identify a renal compromise in a timely manner [58]. Urine protein excretion is also increased during pregnancy, so isolated elevation of proteinuria is not necessarily indicative of active nephritis [7].

Besides physiological changes induced by pregnancy, PE and LN share some clinical and laboratory features like hypertension, proteinuria, and edema, making it difficult to distinguish between the two entities. This distinction is critical since management differs significantly; while LN requires immunosuppressive treatment, in severe PE delivery may be indicated. A detailed evaluation of biomarkers of SLE activity as anti-dsDNA, the low level of complement, active urine sediment (red cells, white cells, and cellular casts), and the presence of extrarenal SLE manifestations may be helpful in the differential diagnosis. In contrast, in pregnant women with a gestational age greater than 22 weeks and absence of sign of SLE activity, the diagnosis of PE is very likely [59].

Clinical, laboratory, and renal biopsy features present in PE and LN are shown in **Table 1**.

4. Impact of SLE on pregnancy outcomes

Despite diagnostic and therapeutic advances, pregnancies in SLE patients are still considered a high-risk condition due to an elevated risk of major obstetric and neonatal complications. A population-based study from 2000 to 2003 found that maternal mortality was 20-fold higher among women with SLE. The risk for serious medical and pregnancy complications during pregnancy was also three- to seven-fold higher for SLE women than the general population [62].

In recent years, outcomes during pregnancy in patients with SLE related to preconceptional counseling, close monitoring during pregnancy, and postpartum and multidisciplinary management have improved [63]. However, according to a recent meta-analysis comparing maternal and fetal outcomes of women with and without SLE, adverse outcomes such as spontaneous abortion (RR, 1.51), PE (RR, 1.91), thromboembolic disease (RR, 11.29), and preterm birth (RR, 3.05) are still more frequent in pregnancies of women with SLE [64]. Additionally, it has been estimated that women with SLE have fewer live births than the general population [65].

In the last two decades, the rate of fetal losses has declined from 43% in the years 1960–1965 to 17% in the period 2000-2003 [66]. Most recent studies reported a pregnancy loss rate of 10–25% in women with SLE [67]. In addition to risk factors associated with pregnancy losses in the general population, such as chromosomal and anatomical abnormalities, specific factors associated with SLE have to be Considered, including thrombocytopenia, antiphospholipid antibody (aPL) positivity or antiphospholipid syndrome (APS), lupus nephritis, and high SLE disease activity [68]. Both low complement and presence of anti-DNA in the second trimester, regardless of clinical activity, have also been associated with a higher rate of fetal loss and preterm delivery [69].

4.1 Antiphospholipid antibodies and pregnancy

The presence of antiphospholipid syndrome (APS) is one of the most important causes for pregnancy loss in women with SLE, manifesting a recurrent pregnancy loss, fetal loss, or stillbirth (pregnancy loss after 20 weeks of gestation) [29]. In addition to recurrent pregnancy loss, APS predisposes pregnant women to late gestational complications associated with impaired placental function, such as PE and fetal growth restriction. Serious complications have been reported in up to 12% of pregnancies in lupus patients. Interestingly, adverse outcomes in pregnancies of SLE women with aPL antibodies can present even during disease remission or mild activity [50].

Antiphospholipid antibodies target the placenta by binding β2 glycoprotein I (β2GPI) constitutively expressed on trophoblast cell surface, perturbing the secretion of trophoblast angiogenic factors in the first trimester of gestation and favoring adverse outcomes [70].

The prevalence of aPL antibodies in patients with SLE is variable and depends on the type of antibodies and isotype. A prevalence of 12–44% of anticardiolipin antibodies (aCL), 15–34% for lupus anticoagulant (LA), and 10–19% for anti-β2 glycoprotein I (aβ2GPI) has been reported [71], although prevalence of aPL could be underestimated due to immunosuppressive treatment. A higher frequency of thrombosis and pregnancy loss in SLE-associated APS (secondary APS) than in primary APS has been reported. Moreover, in the Hopkins lupus cohort, the diagnosis of secondary APS led to a threefold increase in pregnancy loss, especially after 20 weeks of gestation and was an independent risk factor for further pregnancy losses [68].

The association of aPL with adverse pregnancy outcomes (APOs) is variable between different aPL antibodies. Particular serological profiles have been defined as "high-risk profiles" because of its stronger association with APOs. Lupus anticoagulant rather than aCL has been identified as the primary predictor of APOs [72]. In the PROMISSE study, a large-scale multicenter prospective study of pregnant women with aPL and/or underlying stable SLE, a higher rate of APOs in pregnant patients with aPL (43.8%) compared to 15.4% of patients without aPL was observed, while poor pregnancy outcome was observed mainly in LA-positive patients. The presence of LA was identified as a baseline independent predictor of APOs (OR 8.32), while no other aPL antibody independently predicted APO [73]. The EUROAPS registry also reported that the presence of LA, isolated or in combination with aCL and/or aβ2GPI, was the strongest marker related to poor obstetric outcomes [74].

Regarding treatment, there is no current evidence that the management of pregnancy should be different in SLE-associated APS than in primary APS. Actually, treatment of pregnant patients with aPL will depend on the risk profile and history of adverse obstetric events or previous thrombosis. According to this risk, they can be classified into three groups: (a) presence of aPL antibodies in the absence of obstetric or thrombotic events, (b) high-risk profile (LA or triple positivity) or adverse obstetric events, and (c) aPL antibodies and previous thrombosis.

Although increased lupus activity does seem to not increase the risk for miscarriage, stillbirth rate is threefold higher [53]. Additionally, the timing of lupus activity seems to impact the pregnancy loss rate, with activity early in pregnancy being the most dangerous [68].

4.2 Antibodies anti-SSA/Ro and anti-SSB/La and neonatal lupus

Pregnancies exposed to anti-SSA/Ro and anti-SSB/La have an increased risk of developing neonatal lupus (NL), a passively acquired autoimmune disease

mediated by maternal antibodies. There are two main forms of NL: NL erythematosus (NLE) and congenital heart block (CHB). Other less frequent forms include hepatic and hematologic. NLE occurs in 5% of children born to women with anti-Ro/SSA or anti-La antibodies. It usually presents within the first 2 weeks of life as erythematous geographical lesions in light-exposed areas, resembling subacute cutaneous lupus. Rash resolves within 6–8 months of life as the maternal antibodies are cleared, without leaving residual scarring [75]. CHB is a more serious form of NL, affecting 1–2% of newborns of anti-Ro-positive women and a recurrence rate in subsequent pregnancies up to 16–20%. Incomplete forms of CHB have been described, including first-degree heart block that can progress during childhood. Permanent pacemaker will be needed in most children with CHB, and up to 20% may die in the perinatal period [76].

Starting from the second trimester, maternal IgG antibodies are actively transferred via the placental FcRn receptor to the fetus. Although the precise mechanism of injury is not fully known, one hypothesis considers a direct effect of anti-SSA/Ro and/or anti-SSB/La antibodies by binding to fetal cardiac tissue and altering cardiocyte function. In the case of anti-SSA/Ro antibodies, they can bind cross-reactive epitopes on calcium-regulating molecules such as ion channels, inducing disturbances in calcium homeostasis and signal electrogenesis at the atrioventricular node. A demonstration that anti-SSA/Ro antibodies are arrhythmogenic and inhibit inward calcium fluxes across cell membranes supports this hypothesis [77].

Another hypothesis raise that intracellular anti-SSA/Ro and SSB/La antigens translocate to the surface of cardiomyocytes undergoing apoptosis during physiological remodeling and thus become accessible to extracellular antibody. This allows the formation of pathogenic antibody-apoptotic cell immune complexes that promote a pro-inflammatory and profibrotic response [78]. In vitro studies support a protective role of β2GPI by preventing opsonization of apoptotic cardiomyocytes by maternal anti-Ro60 IgG [79].

CHB is usually preceded by lesser degrees of conduction delays which may be reversed with early treatment. Given that the majority of conduction abnormalities develop between 18 and 24 weeks of gestation, several tools for early detection of lesser degrees of heart block are available, including fetal Doppler echocardiography, fetal kinetocardiogram, and transabdominal fetal echocardiography. Close monitoring of anti-SSA/Ro-positive pregnant women with weekly fetal Doppler echocardiography between 16 and 26 weeks of gestation and biweekly thereafter is highly recommended [61]. This enables assessment of atrial and ventricular rates, cardiac anatomy and function, and the presence or absence of hydrops. Urgent referral to a fetal medicine unit or fetal cardiology service is advised if a low fetal heart rate (<110 bpm) is detected. An increased risk of hydrops and death is present if the rate is <55 bpm [76].

Although fetal echocardiogram is the most commonly used modality, it may underestimate pathological findings of NL, so recently other biomarkers for early detection of heart disease and to monitor severity and progression of cardiac LN have been suggested, such as NT-proBNP in amniotic fluid [80].

Different strategies have been evaluated for CHB associated with anti-Ro and/or anti-La antibodies. Prenatal therapy with fluorinated steroids like dexamethasone in mothers of fetuses with incomplete heart block is currently used; however, its role has been questioned since published data are discordant regarding its efficacy. A multiracial/ethnic US-based registry of cardiac neonatal lupus demonstrated that fluorinated steroids do not prevent heart block progression or death in cases with isolated heart block and without evidence of extranodal disease [81]. In a more recent study, the use of fluorinated steroids was not associated with

complete heart block regression or an increase in survival [82]. Therefore, the decision to administer this type of steroid, usually at high doses (at least dexamethasone 4 mg daily), should be weighed against the potential risk of adverse effects on the fetus and the mother [78].

Preventive management of anti-SSA/Ro- and/or anti-La/SSB-positive pregnant women is under investigation. Hydroxychloroquine administration during pregnancy has been associated with a decrease of recurrent NL [83]. On the other hand, recent studies failed to demonstrate efficacy of monotherapy with intravenous immunoglobulin or plasma exchange in reducing the incidence of cardiac NL [84, 85].

5. Contraception, fertility, and assisted reproduction in SLE

Contraception is a complex issue and of particular interest in SLE patients to prevent unplanned pregnancies during periods of disease activity or potentially teratogenic drug exposure. The main concerns about hormonal contraceptive methods are disease flares and risk of thromboembolism [86]. The risk of complications associated with the use of hormonal contraceptives has been evaluated by two randomized clinical trials. A first study compared a combined three-phase oral contraceptive with placebo in 183 patients with SLE. No significant differences in the number of disease flares between both groups were observed [87]. A second study compared a combined oral contraceptive, a progestogen, and non-medicated intrauterine device. Disease activity remained stable during follow-up, and only four thrombosis episodes were recorded, two episodes per hormone treatment group [88]. However, both studies excluded patients with severely active SLE, history of previous thrombosis, malignant gynecological neoplasm, acute myocardial infarction, and previous hepatopathies and patients actively smoking. Regarding aPL antibodies, patients with positivity for these antibodies were excluded in the first study, but not in the second trial. According to both studies, combined hormonal contraceptives (estrogens plus progestogens or progestins alone) are safe in patients with stable SLE in the absence of aPL, without increasing the risk of disease flares of thrombotic events.

Fertility is a relevant topic in SLE patients due to predominance of female gender and reproductive age. The reproductive issue in SLE women does not result from an increase in primary fertility rate but from an increase in the number of fetal losses and use of drugs related to infertility. Cyclophosphamide (CYC) has been associated with ovarian reserve depletion by inducing apoptosis of oocytes and granulosa somatic cells, with the consequent premature ovarian failure in a dose- and age-dependent manner. Although the exact incidence of secondary ovarian failure due to CYC is not clear, it may vary between 11 and 59%, and a higher risk is observed in women older than 30 years [89]. Simultaneous administration of GnRH agonist has been suggested to minimize the gonadotoxic effect of CYC. Other disease-modifying rheumatic drugs (DMARDs) such as mycophenolate mofetil, cyclosporine, or tacrolimus have not been associated with infertility in lupus patients [90].

On the other hand, it has recently been suggested that SLE per se has a negative effect on ovarian function and reserve, regardless of the disease activity and use of gonadotoxic immunosuppressive therapies. A study that measured levels of anti-Müllerian hormone (AMH), a marker of ovarian reserve, in lupus patients and healthy controls found lower levels of AMH in the first group, with no correlation between disease activity and duration [91].

The role of aPL antibodies as a cause of infertility is controversial, as previous retrospective studies have suggested an association between aPL antibodies and infertility. However, two recent studies have not demonstrated a higher prevalence of these antibodies in women with infertility or a correlation with the type of infertility [92, 93].

A strategy to overcome the difficulties of achieving a successful pregnancy is the use of assisted reproduction technologies (ARTs), which includes ovarian stimulation, oocyte retrieval, in vitro fertilization (IVF), and transfer of the embryo to the uterus [94]. Many stimulation protocols are available, but ovarian stimulation with human chorionic gonadotropin (hCG) is the most frequently applied. These hormones determine an estrogenic peak in order to stimulate the growth of multiple follicles, which may increase the risk of multiple pregnancy, preterm birth, and ovarian hyperstimulation syndrome, but the main concern rises around the risk of disease exacerbation or maternal complications. Although the hormonal stimulation could theoretically trigger a disease flare or the onset of thrombosis in patients with aPL antibodies, recent studies have shown that they can be safe and have a low probability of SLE flare [94, 95].

A relevant issue with the use of ARTs is the incidence of thrombotic events. During ovarian stimulation, several changes in coagulation have been described including an increase in fibrinogen, von Willebrand factor, and platelets and decrease in antithrombin III and fibrinolytic activity. These changes may induce a state of relative hypercoagulability. However, the absolute risk of thrombosis during ovarian stimulation is low due to the predominant use of estradiol (E2) and short time of stimulation. The observed incidence is quite low and related to ovarian hyperstimulation syndrome. A systematic review identified as risk factors for thromboembolic complications advanced age (>35 years) and hereditary thrombophilias, while SLE and APS were not independent risk factors [96].

Regarding the efficacy of ART, the success rate varies from 16 to 31% in women with SLE, similar to the general population [48]. The role of aPL has been examined by previous retrospective studies that suggested a relationship between aPL positivity, infertility, and multiple failures of ART procedures. However, recent evidence does not support this since the presence of aPL antibodies has not been identified as a predictor of failure during the use of ART [97]. In a prospective study of 101 infertile women with at least three unsuccessful IVF attempts, no association was found between aPL positivity and success rate [98].

Despite the lack of studies evaluating the risks and benefits of different ovarian stimulation protocols, it is suggested to avoid high serum concentration of estradiol. In the case of anovulation, ovarian induction with clomiphene citrate represents the first choice. In treatment failure, pulsatile administration of GnRH over the use of gonadotropins is preferred since the latter does not confer the risk of ovarian hyperstimulation syndrome [91].

The period of the highest risk is not ovarian stimulation but pregnancy due to elevated rates of fetal and maternal complication, so the main reason for rejecting ART in women with SLE is foremost the risk of obstetric and maternal adverse outcomes. ART is safe in patients with stable SLE; however, its use is not recommended in patients with active SLE, uncontrolled hypertension, chronic kidney disease, severe valve disease, or severe thromboembolic events [48].

6. Algorithm in women with SLE

An algorithm proposal to approach women with SLE of childbearing age is presented in **Figure 1**.

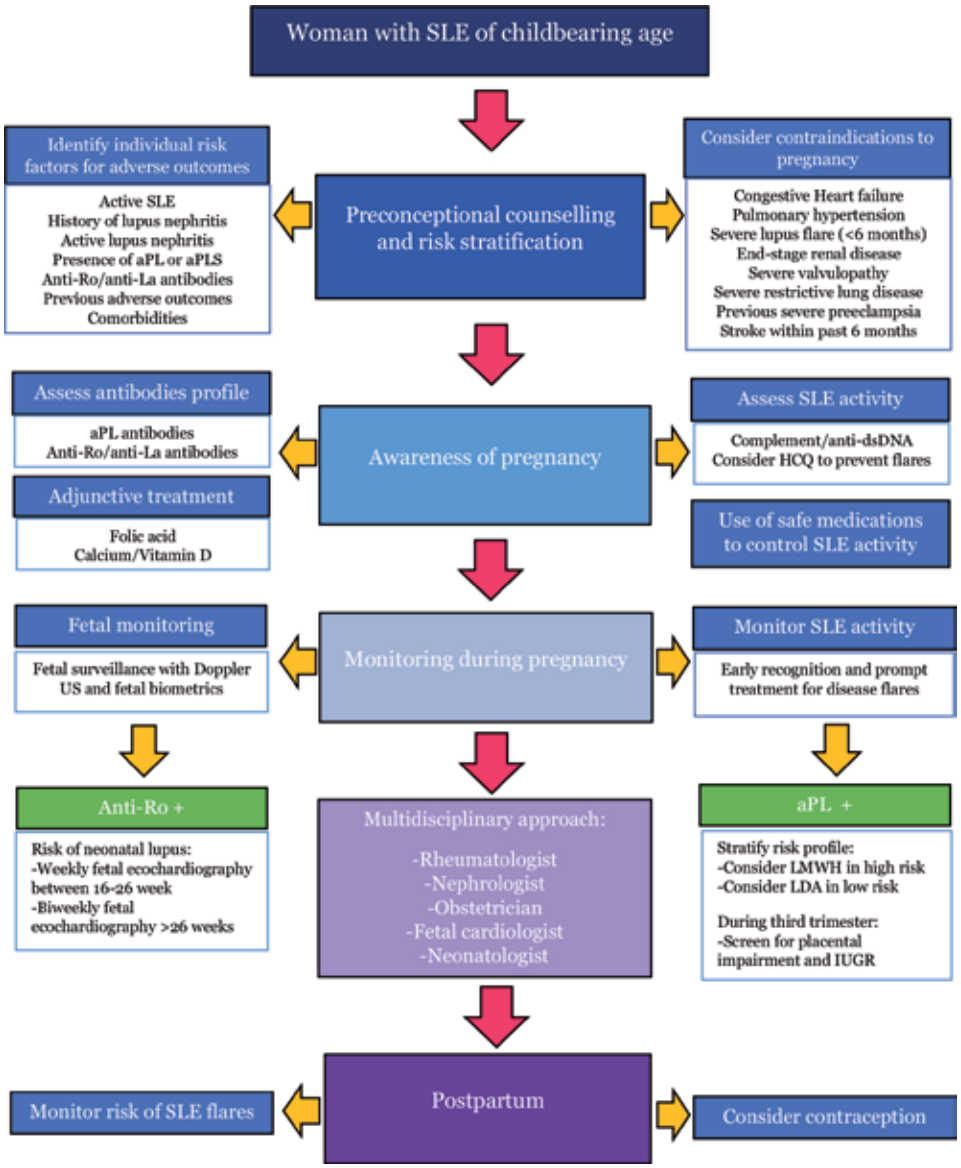


Figure 1.
Approach to pregnant woman with SLE. Data from [76, 99]. aPL, antiphospholipid; LMWH, low-molecular-weight heparin; LDA, low-dose aspirin; IUGR, intrauterine growth restriction.

7. Conclusions

Pregnancy induces immunologic and hormonal adaptations on a pregnant woman to permit maternal tolerance to the fetus. The balance between Th17 cells and Treg cells seems critical to pregnancy outcomes, although its possible implication in maternal-fetal complications in SLE woman is not completely understood.

The relationship between SLE and pregnancy is close and bidirectional; active disease is associated with the increased risk of adverse pregnancy outcomes and pregnancy changes which impact on maternal disease triggering flares during this period.

Besides disease activity, immunologic factors related to SLE such as aPL and anti-SSA/Ro antibodies can also influence obstetric and neonatal outcomes. The

presence of aPL antibodies is one of the most important risk factors for pregnancy loss and late gestational complications in women with SLE. Treatment of pregnant patients with aPL will depend on the risk profile and history of obstetric or thrombotic events. Anti-SSA/Ro antibodies are related to neonatal lupus due to active transplacental transfer of these antibodies possibly causing direct injury to the cardiac conduction system manifesting as congenital heart block. Fetal Doppler echocardiographic monitoring between 16 and 26 weeks of gestation is highly recommended in pregnant women with anti-SSA/Ro for early detection of heart conduction delays.

Combined hormonal contraceptives are safe in women with stable SLE in the absence of aPL, without an increasing risk of disease flares or thrombotic events. Fertility in women with lupus can be affected not only by exposure to drugs related to infertility but also by SLE per se.

Acknowledgements

This work was supported by the National Institute of Medical Science and Nutrition SZ Grants [INCMNSZ-AI-024 (JRD)] and the National Council of Science and Technology [CONACYT SALUD-214395 (JRD)].

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this chapter.

Author details

María del Carmen Zamora-Medina and Juanita Romero-Díaz*
Department of Immunology and Rheumatology, National Institute of Medical Science and Nutrition Salvador Zubiran, Mexico City, Mexico

*Address all correspondence to: juanita.romerodiaz@gmail.com

References

[1] Munoz-Suano A, Hamilton AB, Betz AG. Gimme shelter: The immune system during pregnancy. Immunological Reviews. 2011;**241**:20-38. DOI: 10.1111/j.1600-065X.2011.01002.x

[2] Østensen MM, Villiger PM, Förger F. Interaction of pregnancy and autoimmune rheumatic disease. Autoimmunity Reviews. 2012;**11**:A437-A446. DOI: 10.1016/j.autrev.2011.11.013

[3] Østensen M, Förger F, Villiger PM. Cytokines and pregnancy in rheumatic disease. Annals of the New York Academy of Sciences. 2006;**1069**:353-363

[4] Chaouat G, Ledée-Bataille N, Dubanchet S, Zourbas S, Sandra O, Martal J. TH1/TH2 paradigm in pregnancy: Paradigm lost? Cytokines in pregnancy/early abortion: Reexamining the TH1/TH2 paradigm. International Archives of Allergy and Immunology. 2004;**134**:93-119

[5] Bianchi DW, Zickwolf GK, Weil GJ, Sylvester S, DeMaria MA. Male fetal progenitor cells persist in maternal blood for as long as 27 years postpartum. Proceedings of the National Academy of Sciences of the United States of America. 1996;**93**:705-708

[6] Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. Immunological Investigations. 2008;**37**:631-644. DOI: 10.1080/08820130802205886

[7] de Jesus GR, Mendoza-Pinto C, de Jesus NR, et al. Understanding and managing pregnancy in patients with lupus. Autoimmune Disease. 2015;**2015**:943490. DOI: 10.1155/2015/943490

[8] Denney JM, Nelson EL, Wadhwa PD, et al. Longitudinal modulation of immune system cytokine profile during pregnancy. Cytokine. 2011;**53**:170-177. DOI: 10.1016/j.cyto.2010.11.005

[9] Elenkov IJ, Wilder RL, Bakalov VK, et al. IL-12, TNF-alpha, and hormonal changes during late pregnancy and early postpartum: Implications for autoimmune disease activity during these times. The Journal of Clinical Endocrinology and Metabolism. 2001;**86**:4933-4938

[10] Ekerfelt C, Matthiesen L, Berg G, Ernerudh J. Paternal leukocytes selectively increase secretion of IL-4 in peripheral blood during normal pregnancies: Demonstrated by a novel one-way MLC measuring cytokine secretion. American Journal of Reproductive Immunology. 1997;**38**:320-326

[11] Matthiesen L, Ekerfelt C, Berg G, Ernerudh J. Increased numbers of circulating interferon-gamma- and interleukin-4-secreting cells during normal pregnancy. American Journal of Reproductive Immunology. 1996;**39**:362-367

[12] Cutolo M, Sulli A, Capellino S, et al. Sex hormones influence on the immune system: Basic and clinical aspects in autoimmunity. Lupus. 2004;**13**:635-638

[13] Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. Nature Immunology. 2004;**5**:266-271

[14] La Rocca C, Carbone F, Longobardi S, Matarese G. The immunology of pregnancy: Regulatory T cells control maternal immune tolerance toward the fetus. Immunology Letters. 2014;**162**: 41-48. DOI: 10.1016/j.imlet.2014.06.013

[15] Somerset DA, Zheng Y, Kilby MD, Sansom DM, Drayson MT. Normal human pregnancy is associated with an elevation in the immune suppressive

CD25+ CD4+ regulatory T-cell subset. Immunology. 2004;**112**:38-43

[16] Tower C, Crocker I, Chirico D, Baker P, Bruce I. SLE and pregnancy: The potential role for regulatory T cells. Nature Reviews Rheumatology. 2011;**7**:124-128. DOI: 10.1038/nrrheum.2010.124

[17] Schumacher A, Wafula PO, Bertoja AZ, et al. Mechanisms of action of regulatory T cells specific for paternal antigens during pregnancy. Obstetrics and Gynecology. 2007;**110**:1137-1145

[18] Alijotas-Reig J, Llurba E, Gris JM. Potentiating maternal immune tolerance in pregnancy: A new challenging role for regulatory T cells. Placenta. 2014;**35**:241-248. DOI: 10.1016/j.placenta.2014.02.004

[19] Zhou J, Wang J, Zhao X, Wang J, Sun H, Hu Y. An increase of treg cells in the peripheral blood is associated with a better in vitro fertilization treatment outcome. American Journal of Reproductive Immunology. 2012;**68**:100-106. DOI: 10.1111/j.1600-0897.2012.01153.x

[20] Mold JE, Michaëlsson J, Burt TD, et al. Maternal alloantigens promote the development of tolerogenic fetal regulatory T cells in utero. Science. 2008;**322**:1562-1565. DOI: 10.1126/science.1164511

[21] Varthese S, Crocker I, Bruce IN, Tower C. Systemic lupus erythematosus, regulatory T cells and pregnancy. Expert Review of Clinical Immunology. 2011;**7**:635-648. DOI: 10.1586/eci.11.59

[22] Bettelli E, Carrier Y, Gao W, et al. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. Nature. 2006;**441**:235-238

[23] Mjösberg J, Berg G, Jenmalm MC, Ernerudh J. FOXP3+ regulatory T cells and T helper 1, T helper 2, and T helper 17 cells in human early pregnancy decidua. Biology of Reproduction. 2010;**82**:698-705. DOI: 10.1095/biolreprod.109.081208

[24] Santner-Nanan B, Peek MJ, Khanam R, et al. Systemic increase in the ratio between Foxp3+ and IL-17-producing CD4+ T cells in healthy pregnancy but not in preeclampsia. Journal of Immunology. 2009;**183**:7023-7030. DOI: 10.4049/jimmunol.0901154

[25] Toldi G, Rigó J Jr, Stenczer B, Vásárhelyi B, Molvarec A. Increased prevalence of IL-17-producing peripheral blood lymphocytes in pre-eclampsia. American Journal of Reproductive Immunology. 2011;**66**:223-229. DOI: 10.1111/j.1600-0897.2011.00987.x

[26] Wang WJ, Hao CF, Yi-Lin, et al. Increased prevalence of T helper 17 (Th17) cells in peripheral blood and decidua in unexplained recurrent spontaneous abortion patients. Journal of Reproductive Immunology. 2010;**84**:164-170. DOI: 10.1016/j.jri.2009.12.003

[27] Nakashima A, Ito M, Shima T, Bac ND, Hidaka T, Saito S. Accumulation of IL-17-positive cells in decidua of inevitable abortion cases. American Journal of Reproductive Immunology. 2010;**64**:4-11. DOI: 10.1111/j.1600-0897.2010.00812.x

[28] Doria A, Ghiradello A, Iaccarino L, et al. Pregnancy, cytokines, and disease activity in systemic lupus erythematosus. Arthritis and Rheumatism. 2004;**51**:989-995

[29] Ostensen M, Clowse M. Pathogenesis of pregnancy complications in systemic lupus erythematosus. Current Opinion in Rheumatology. 2013;**25**:591-596. DOI: 10.1097/BOR.0b013e328363ebf7

[30] Muñoz-Valle JF, Vázquez-Del Mercado M, García-Iglesias T, et al. T(H)1/T(H)2 cytokine profile, metalloprotease-9 activity and hormonal status in pregnant rheumatoid arthritis and systemic lupus erythematosus patients. Clinical and Experimental Immunology. 2003;**131**:377-384

[31] Baráth S, Soltész P, Kiss E, et al. The severity of systemic lupus erythematosus negatively correlates with the increasing number of CD4+CD25(high)FoxP3+ regulatory T cells during repeated plasmapheresis treatments of patients. Autoimmunity. 2007;**40**:521-528

[32] Bonelli M, Savitskaya A, von Dalwigk K, et al. Quantitative and qualitative deficiencies of regulatory T cells in patients with systemic lupus erythematosus (SLE). International Immunology. 2008;**20**:861-868. DOI: 10.1093/intimm/dxn044

[33] Valencia X, Yarboro C, Illei G, Lipsky PE. Deficient CD4+CD25 high T regulatory cell function in patients with active systemic lupus erythematosus. Journal of Immunology. 2007;**178**:2579-2588

[34] Lee HY, Hong YK, Yun HJ, Kim YM, Kim JR, Yoo WH. Altered frequency and migration capacity of CD4+CD25+ regulatory T cells in systemic lupus erythematosus. Rheumatology (Oxford). 2008;**47**:789-794. DOI: 10.1093/rheumatology/ken108

[35] Vargas-Rojas MI, Crispín JC, Richaud-Patin Y, Alcocer-Varela J. Quantitative and qualitative normal regulatory T cells are not capable of inducing suppression in SLE patients due to T-cell resistance. Lupus. 2008;**17**:289-294. DOI: 10.1177/0961203307088307

[36] Ma J, Yu J, Tao X, Cai L, Wang J, Zheng SG. The imbalance between regulatory and IL-17-secreting CD4+ T cells in lupus patients. Clinical Rheumatology. 2010;**29**:1251-1258. DOI: 10.1007/s10067-010-1510-7

[37] Xing Q, Wang B, Su H, Cui J, Li J. Elevated Th17 cells are accompanied by FoxP3+ treg cells decrease in patients with lupus nephritis. Rheumatology International. 2012;**32**:948-958. DOI: 10.1007/s00296-010-1771-0

[38] Torricelli M, Bellisai F, Novembri R, et al. High levels of maternal serum IL-17 and activin A in pregnant women affected by systemic lupus erythematosus. American Journal of Reproductive Immunology. 2011;**66**:84-89. DOI: 10.1111/j.1600-0897.2011.00978.x

[39] Becker-Merok A, Eilertsen GØ, Nossent JC. Levels of transforming growth factor-beta are low in systemic lupus erythematosus patients with active disease. The Journal of Rheumatology. 2010;**37**:2039-2045. DOI: 10.3899/jrheum.100180

[40] Jara LJ, Pacheco-Reyes H, Medina G, Angeles U, Cruz-Cruz P, Saavedra MA. Prolactin levels are associated with lupus activity, lupus anticoagulant, and poor outcome in pregnancy. Annals of the New York Academy of Sciences. 2007;**1108**:218-226

[41] Leaños-Miranda A, Cárdenas-Mondragón G, Ulloa-Aguirre A, Isordia-Salas I, Parra A, Ramírez-Peredo J. Anti-prolactin autoantibodies in pregnant women with systemic lupus erythematosus: Maternal and fetal outcome. Lupus. 2007;**16**:342-349

[42] Jara LJ, Cruz-Cruz P, Saavedra MA, et al. Bromocriptine during pregnancy in systemic lupus erythematosus: A pilot clinical trial. Annals of the New York Academy of Sciences. 2007;**11110**:297-304

[43] Qian Q, Liugin L, Hao L, et al. The effects of bromocriptine on

preventing postpartum flare in systemic lupus erythematosus patients from South China. Journal of Immunology Research. 2015;**2015**:316955. DOI: 10.1155/2015/316965

[44] Zen M, Ghirardello A, Iaccarino L, et al. Hormones, immune response, and pregnancy in healthy women and SLE patients. Swiss Medical Weekly. 2010;**140**:187-201. DOI: smw-12597

[45] Tavakolpour S, Rahimzadeh G. New insights into the management of patients with autoimmune diseases or inflammatory disorders during pregnancy. Scandinavian Journal of Immunology. 2016;**84**:146-149. DOI: 10.1111/sji.12453

[46] Clowse ME. Lupus activity in pregnancy. Rheumatic Diseases Clinics of North America. 2007;**33**:237-252

[47] Cortés-Hernández J, Ordi-Ros J, Paredes F, Casellas M, Castillo F, Vilardell-Tarres M. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: A prospective study of 103 pregnancies. Rheumatology (Oxford, England). 2002;**41**:643-650. DOI: 10.1093/rheumatology/41.6.643

[48] Lazzaroni MG, Dall'Ara F, Fredi M, et al. A comprehensive review of the clinical approach to pregnancy and systemic lupus erythematosus. Journal of Autoimmunity. 2016;**74**:106-117. DOI: 10.1016/j.jaut.2016.06.016

[49] Jara LJ, Medina G, Cruz-Dominguez P, Navarro C, Vera-Lastra O, Saavedra MA. Risk factors of systemic lupus erythematosus flares during pregnancy. Immunologic Research. 2014;**60**:184-192. DOI: 10.1007/s12026-014-8577-1

[50] Clowse ME, Magder LS, Witter F, Petri M. The impact of increased lupus activity on obstetric outcomes. Arthritis and Rheumatism. 2005;**52**:514-521

[51] Andrade RM, McGwin G Jr, Alarcon GS, et al. Predictors of post-partum damage accrual in systemic lupus erythematosus: Data from LUMINA, a multiethnic US cohort (XXXVIII). Rheumatology (Oxford, England). 2006;**45**:1380-1384

[52] Clowse ME, Magder L, Witter F, Petri M. Hydroxychloroquine in lupus pregnancy. Arthritis and Rheumatism. 2006;**54**:3640-3647

[53] Saavedra M, Sánchez A, Morales S, Navarro-Zarza JE, Ángeles U, Jara LJ. Primigravida is associated with flare in women with systemic lupus erythematosus. Lupus. 2015;**24**:180-185. DOI: 10.1177/0961203314552116

[54] Saavedra MA, Cruz-Reyes C, Vera-Lastra O, et al. Impact of previous lupus nephritis on maternal and fetal outcomes during pregnancy. Clinical Rheumatology. 2012;**31**:813-819. DOI: 10.1007/s10067-012-1941-4

[55] Moroni G, Doria A, Giglio E, et al. Maternal outcome in pregnant women with lupus nephritis. A prospective multicenter study. Journal of Autoimmunity. 2016;**74**:194-200. DOI: 10.1016/j.jaut.2016.06.012

[56] Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clinical Journal of the American Society of Nephrology. 2010;**5**:2060-2068. DOI: 10.2215/CJN.00240110

[57] Bramham K, Hunt BJ, Bewley S, et al. Pregnancy outcomes in systemic lupus erythematosus with and without previous nephritis. The Journal of Rheumatology. 2011;**38**:1906-1913. DOI: 10.3899/jrheum.100997

[58] Conrad KP, Davison JM. The renal circulation in normal pregnancy

and preeclampsia: Is there a place for relaxin? American Journal of Physiology. Renal Physiology. 2014;**306**:1121-1135. DOI: 10.1152/ajprenal.00042.2014

[59] Stanhope TJ, White WM, Moder KG, Smyth A, Garovic VD. Obstetric nephrology: Lupus and lupus nephritis in pregnancy. Clinical Journal of the American Society of Nephrology. 2012;**7**:2089-2099. DOI: 10.2215/CJN.12441211

[60] Kattah AG, Garovic VD. Pregnancy and lupus nephritis. Seminars in Nephrology. 2015;**35**(5):487-499. DOI: 10.1016/j.semnephrol.2015.08.010

[61] Lightstone L, Hladunewich MA. Lupus nephritis and pregnancy: Concerns and management. Seminars in Nephrology. 2017;**37**(4):347-353. DOI: 10.1016/j.semnephrol.2017.05.006

[62] Clowse ME, Jamison M, Myers E, James AH. A national study of the complications of lupus in pregnancy. American Journal of Obstetrics and Gynecology. 2008;**199**:127.e1-127.e6. DOI: 10.1016/j.ajog.2008.03.012

[63] Lateef A, Petri M. Systemic lupus erythematosus and pregnancy. Rheumatic Diseases Clinics of North America. 2017;**43**:215-226. DOI: 10.1016/j.rdc.2016.12.009

[64] Bundhun PK, Soogund MZ, Huang F. Impact of systemic lupus erythematosus on maternal and fetal outcomes following pregnancy: A meta-analysis of studies published between years 2001-2016. Journal of Autoimmunity. 2017;**79**:17-27. DOI: 10.1016/j.jaut.2017.02.009

[65] Vinet E, Clarke AE, Gordon C, et al. Decreased live births in women with systemic lupus erythematosus. Arthritis Care & Research. 2011;**63**:1068-1072. DOI: 10.1002/acr.20466

[66] Clark CA, Spitzer KA, Laskin CA. Decrease in pregnancy loss rates in patients with systemic lupus erythematosus over a 40-year period. The Journal of Rheumatology. 2005;**32**:1709-1712

[67] Andreoli L, Crisafulli F, Tincani A. Pregnancy and reproductive aspects of systemic lupus erythematosus. Current Opinion in Rheumatology. 2017;**29**:473-479. DOI: 10.1097/BOR.0000000000000415

[68] Clowse ME, Magder LS, Witter F, Petri M. Early risk factors for pregnancy loss in lupus. Obstetrics and Gynecology. 2006;**107**:293-299

[69] Clowse ME, Magder LS, Petri M. The clinical utility of measuring complement and anti-dsDNA antibodies during pregnancy in patients with systemic lupus erythematosus. The Journal of Rheumatology. 2011;**38**: 1012-1016. DOI: 10.3899/jrheum.100746

[70] Carroll TY, Mulla MJ, Han CS, et al. Modulation of trophoblast angiogenic factor secretion by antiphospholipid antibodies is not reversed by heparin. American Journal of Reproductive Immunology. 2011;**66**:286-296. DOI: 10.1111/j.1600-0897.2011.01007.x

[71] Biggioggero M, Meroni PL. The geoepidemiology of the antiphospholipid antibody syndrome. Autoimmunity Reviews. 2010;**9**:A299-A304. DOI: 10.1016/j.autrev.2009.11.013

[72] Lockshin MD, Kim M, Laskin CA, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis and Rheumatism. 2012;**64**:2311-2318. DOI: 10.1002/art.34402

[73] Buyon JP, Kim MY, Guerra MM, et al. Predictors of pregnancy outcomes

in patients with lupus: A cohort study. Annals of Internal Medicine. 2015;**163**:153-163. DOI: 10.7326/M14-2235

[74] Alijotas-Reig J, Ferrer-Oliveras R, Ruffatti A, et al. The european registry on obstetric antiphospholipid syndrome (EUROAPS): A survey of 247 consecutive cases. Autoimmunity Reviews. 2015;**14**:387-395. DOI: 10.1016/j.autrev.2014.12.010

[75] Brucato A, Cimaz R, Caporali R, Ramoni V, Buyon J. Pregnancy outcomes in patients with autoimmune diseases and anti-Ro/SSA antibodies. Clinical Reviews in Allergy and Immunology. 2011;**40**:27-41. DOI: 10.1007/s12016-009-8190-6

[76] Knight CL, Nelson-Piercy C. Management of systemic lupus erythematosus during pregnancy: Challenges and solutions. Open access Rheumatology: Research and Reviews. 2017;**9**:37-53. DOI: 10.2147/OARRR.S87828

[77] Buyon JP, Kim MY, Copel JA, Friedman DM. Anti-Ro/SSA antibodies and congenital heart block: Necessary but not sufficient. Arthritis and Rheumatism. 2001;**44**:1723-1727

[78] Izmirly PM, Buyon JP, Saxena A. Neonatal lupus: Advances in understanding pathogenesis and identifying treatments of cardiac disease. Current Opinion in Rheumatology. 2012;**24**:466-472. DOI: 10.1097/BOR.0b013e328356226b[80]

[79] Reed JH, Clancy RM, Purcell AW, et al. B2-glycoprotein 1 and protection from anti-SSA/Ro60-associated cardiac manifestations of neonatal lupus. Journal of Immunology. 2011;**187**:520-526. DOI: 10.4049/jimmunol.1100122

[80] Saxena A, Izmirly PM, Han SW, et al. Serum biomarkers of inflammation, fibrosis, and cardiac function in facilitating diagnosis, prognosis, and treatment of anti-SSA/Ro associated cardiac neonatal lupus. Journal of the American College of Cardiology. 2015;**66**:930-939. DOI: 10.1016/j.jacc.2015.06.1088

[81] Izmirly PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multiracial/ethnic registry of anti-SSA/Ro associated cardiac neonatal lupus. Circulation. 2011;**124**:1927-1935. DOI: 10.1161/CIRCULATIONAHA.111.033894

[82] Levesque K, Morel N, Maltret A, et al. Description of 214 cases of autoimmune congenital heart block: Results of the French neonatal lupus syndrome. Autoimmunity Reviews. 2015;**14**:1154-1160. DOI: 10.1016/j.autrev.2015.08.005

[83] Izmirly PM, Costedoat-Chalumeau N, Pisoni C, et al. Maternal use of hydroxychloroquine is associated with a reduced risk of recurrent anti-SSA/Ro associated cardiac manifestations of neonatal lupus. Circulation. 2012;**3**(126):76-82. DOI: 10.1161/CIRCULATION AHA.111.089268

[84] Friedman DM, Llanos C, Izmirly PM, et al. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. Arthritis and Rheumatism. 2010;**62**:1138e1146. DOI: 10.1002/art.27308

[85] Makino S, Yonemoto H, Itoh S, Takeda S. Effect of steroid administration and plasmapheresis to prevent fetal congenital heart block in patients with systemic lupus erythematosus and/or Sjögren's syndrome. Acta Obstetricia et Gynecologica Scandinavica. 2007;**86**:1145-1146

[86] Chowdhary VR. Broad concepts in management of systemic lupus erythematosus. Mayo Clinic Proceedings. 2017;**92**:744-761. DOI: 10.1016/j.mayocp.2017.02.007

[87] Buyon JP, Petri MA, Kim MY, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: A randomized trial. Annals of Internal Medicine. 2005;**142**:953-962

[88] Sanchez-Guerrero J, Uribe AG, Jimenez-Santana L, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. The New England Journal of Medicine. 2005;**353**:2539-2549

[89] Janssen NM, Genta MS. The effects of immunosuppressive and anti-inflammatory medications on fertility, pregnancy, and lactation. Archives of Internal Medicine. 2000;**160**:610-619

[90] Lawrenz B, Henes J, Henes M, et al. Impact of systemic lupus erythematosus on ovarian reserve in premenopausal women: Evaluation by using anti-Mullerian hormone. Lupus. 2011;**20**:1193-1197. DOI: 10.1177/0961203311409272

[91] Cervera R, Balasch J. Bidirectional effects on autoimmunity and reproduction. Human Reproduction Update. 2008;**14**:359-366. DOI: 10.1177/0961203311409272

[92] Levine AB, Lockshin MD. Assisted reproductive technology in SLE and APS. Lupus. 2014;**23**:1239-1241. DOI: 10.1177/0961203314527370

[93] Steinvil A, Raz R, Berliner S, et al. Association of common thrombophilias and antiphospholipid antibodies with success rate of in vitro fertilisation. Thrombosis and Haemostasis. 2012;**108**:1192-1197. DOI: 10.1160/TH12-06-0381

[94] Bellver J, Pellicer A. Ovarian stimulation for ovulation induction and in vitro fertilization in patients with systemic lupus erythematosus and antiphospholipid syndrome. Fertility and Sterility. 2009;**92**:1803-1810. DOI: 10.1016/j.fertnstert.2009.06.033

[95] Chilcott IT, Margara R, Cohen H, et al. Pregnancy outcome is not affected by antiphospholipid antibody status in women referred for in vitro fertilization. Fertility and Sterility. 2000;**73**:526-530

[96] Chan WS, Dixon ME. The "ART" of thromboembolism: A review of assisted reproductive technology and thromboembolic complications. Thrombosis Research. 2008;**121**:713-726

[97] Buckingham K, Chamley L. A critical assessment of the role of antiphospholipid antibodies in infertility. Journal of Reproductive Immunology. 2009;**80**:132-145. DOI: 10.1016/j.jri.2008.11.005

[98] Sanmarco M, Bardin N, Camoin L, et al. Antigenic profile, prevalence, and clinical significance of antiphospholipid antibodies in women referred for in vitro fertilization. Annals of the New York Academy of Sciences. 2007;**1108**:457-465

[99] Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Annals of the Rheumatic Diseases. 2017;**76**(3):476-485. DOI: 10.1136/annrheumdis-2016-209770

Chapter 5

Lupus Pregnancy: Risk Factors and Management

Jose Ordi-Ros, Cristina Sole Marce and Josefina Cortes-Hernandez

Abstract

Systemic lupus erythematosus (SLE) mainly affects women in the fertile age of life. A patient with SLE is as fertile as the general population except for treatment with drugs with ovarian toxicity, severe flare of the disease, or autoimmune oophoritis for anti-ovarian antibodies. Pregnancy in a woman with SLE implies greater maternal and fetal mortality and morbidity. Fetal loss, premature birth, intrauterine growth restriction associated with antiphospholipid antibodies (aPL), and neonatal lupus associated with anti-Ro are important fetal problems. Similarly, preeclampsia and lupus nephritis may lead to diagnostic confusion. Treatment options during pregnancy are limited to a few safe medications, which further restricts options. The loss of refractory pregnancy associated with antiphospholipid antibodies and the complete heart block associated with anti-Ro antibodies remain unresolved problems. The planning of pregnancy with sustainable treatments during pregnancy, no flare of SLE in the previous 6 months, and absence of nephritis are important for a good maternal and fetal prognosis. A gestation planning, multidisciplinary approach, and close monitoring are essential to obtain optimal results.

Keywords: lupus, pregnancy, fertility, antibody, treatment

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that predominantly affects women of fertile age. Pregnancy causes concern for the majority of patients with SLE. The risk of the disease flare during pregnancy, the possibility of fetal loss, and the safety of drugs during pregnancy are of concern. A better understanding of the pathogenesis of SLE and good use of immunosuppressive drugs allows us to better control the disease, and we should not deprive patients with SLE of the opportunity to have children. Prepregnancy information and collaboration between specialists, such as obstetricians and perinatologists, are essential to optimize maternal and fetal outcomes in SLE pregnancies. In this chapter, important issues related to fertility, optimal time of conception, risk of disease flare during pregnancy, course of pregnancy, fetal outcome, safety of various medications used to control SLE during pregnancy and lactation, and a contraceptive education are discussed [1].

2. Systemic lupus erythematosus fertility

Fertility in patients with SLE is not greatly affected by the diagnosis of the disease. The decrease in fertility in SLE can be a consequence of the drugs used in the treatment of these patients, the flare of the disease, the organic damage caused by the disease, or advanced age. The use of cyclophosphamide (CYC) induces the majority of nonage-related infertility in patients with SLE, although the increasing use of mycophenolate mofetil (MMF) for the treatment of renal and extrarenal manifestations reduces the incidence due to its null ovarian toxicity. The risk of infertility due to CYC is associated with both the cumulative dose and an older age (>37 years old) of the woman at the time of treatment. The probability of maintaining fertility after treatment is greater for patients under 30 years of age, six or less monthly intravenous pulses, a cumulative dose of less than 7 g, and lack of amenorrhea before or during drug administration. It is less likely that other treatments in SLE have a significant impact on fertility, although nonsteroidal anti-inflammatory drugs (NSAIDs) have been suggested as possible contributors to infertility and it is suggested that high doses of corticosteroids have some effect on the cycle menstrual through its effect on the hypothalamic pituitary axis (HPA).

Patients with SLE may have menstrual disturbances or even amenorrhea secondary to very active disease. In addition, serum levels of anti-mulleriana hormone (AMH) are lower in patients with SLE not treated with CYC than in controls matched by age. It is important to emphasize that renal failure induced by lupus glomerulonephritis can cause hypofertility or infertility due to an alteration of the HPA, which can be reversed with kidney transplantation.

The profile of autoantibodies does not seem to affect fertility in women with SLE. However, the study of aPL in women with lupus is essential for predicting gestational risk, although recent controlled studies do not support an association between aPL and infertility or in vitro deficient fertilization (IVF). Evaluation or treatment of aPL in infertile women is not recommended.

Older age is an important factor of infertility in SLE, as it is in the general population. Female fertility decreases with age due to the progressive loss of the ovarian reserve; many patients with SLE are older when they try to conceive and may encounter difficulties related to age. The onset of SLE is more frequent in the first years of reproduction, and it is advised to avoid pregnancy when the disease is active. Premature ovarian failure (persistent amenorrhea with elevated levels of follicle-stimulating hormone before age 40) may be of autoimmune etiology in the general population but is rarely associated with systemic autoimmune diseases such as SLE [1, 2]. The study of anti-ovarian antibodies has contributed little to this pathology. However, treatment with corticosteroids and/or immunosuppressants has reversed the process in some cases.

2.1 SLE fertility preservation

Preserving fertility in women with SLE involves limiting cytotoxic drugs when possible and protecting the ovaries during treatment; however, prompt and effective therapy for a severe disease often takes precedence. The cryopreservation of oocytes or embryos is an effective option but requires ovarian stimulation, which may be impractical given the usual need to institute therapy quickly to avoid damage, as well as the risk of hyperstimulation in a patient with active SLE. The age of the patient to whom CYC is administered is not modifiable, but an effort must be made to minimize the total dose of CYC. The use of MMF may be the best option. Treatment with agonists of the gonadotrophic hormone receptor (GnRH) during

CYC therapy to minimize ovarian toxicity has become a common practice. Ovarian toxicity amenorrhea due to CYC has been the classic clinical sign. Now, the measurement of the AMH provides us with a better evaluation of the ovarian reserve. In a study of patients with SLE who received leuprolide with a GnRH agonist between 10 and 14 days before the CYC pulse therapy, a 68% increase in the ovarian reserve was estimated compared to patients with SLE who had not received this treatment. The GnRH agonist should not be administered immediately before the CYC. When administered during the follicular phase of the cycle, it can stimulate the ovaries and worsen ovarian damage. Patients without therapy with GnRH agonists before their first infusion can start treatment after the first cycle and receive treatment at monthly intervals thereafter [2].

3. Contraception control

SLE patients may be strongly advised to avoid pregnancy, particularly when they have severe disease-related damage or active disease or are taking teratogenic medications. Consequently, contraceptive options should be discussed with all female patients of reproductive age. Counseling patients to defer pregnancy relies on the assumption that they will utilize safe and effective contraception. In practice, SLE patients currently underutilize effective contraception, even those taking teratogenic medications [2]. Contraceptives vary in safety and efficacy. Long-acting reversible contraceptives such as intrauterine devices (IUDs) or subdermal implants have the greatest efficacy. IUDs generally contain either progesterone (levonorgesterol) or copper. Although IUDs have a low risk of infection, patients treated with immunosuppressive medications have not been specifically studied. However, HIV-infected women who have been studied do not have a greater risk of infection. Combined hormonal contraceptives include the pill, transdermal patch, and vaginal ring. Serious side effects include a three- to fivefold increased risk of venous thromboembolism and a twofold increased stroke risk. Medications commonly used for patients with SLE, such as warfarin and MMF, may interact with these agents and alter their efficacy. Concern regarding estrogen-induced flare previously has limited the use of oral contraceptives in patients with SLE. Two recent prospective studies in women with stable SLE showed no increased risk of flare with combined oral contraceptives. But oral contraceptives containing the progestin drospirenone can increase serum potassium and be dangerous in patients with nephritis or who also take angiotensin-converting enzyme (ACE) inhibitors. The vaginal ring and the patch may further increase thrombosis risk compared to oral combined contraceptives, and their safety in SLE has not been studied. No forms of estrogen-containing contraceptives are advised for use in aPL-positive patients due to the increased risk for thrombosis [3]. Progesterone-only contraceptives include oral and intramuscular forms, IUDs, and a subdermal etonogestrel implant. Depot medroxyprogesterone acetate (DMPA) injections may decrease bone density when used chronically, a concern in corticosteroid-treated patients. Progesterone-only contraceptives represent a safe and effective option for aPL-positive patients; with the possible exception of DMPA, the risk for thromboembolism is very low, and they may decrease menstrual blood loss. Emergency contraception can be considered for all SLE patients, including aPL-positive patients. Long-acting reversible contraceptives are preferable for most SLE patients, but every decision regarding contraception must balance the risk and efficacy of the method with the risk of unplanned pregnancy.

4. Fertility and assisted reproductive techniques

Fertility is generally unimpaired in patients with systemic lupus erythematosus (SLE), unless they have been treated with cyclophosphamide (CYC). Although CYC is less commonly used for nephritis than in the past because of the availability of MMF, prevention of CYC-induced infertility remains an important concern. Concurrent gonadotropin-releasing hormone (GnRH) analogue therapy, usually leuprolide, appears to decrease risk of premature ovarian failure by CYC. Embryo and oocyte cryopreservation is options to preserve fertility in patients who are stable enough to safely undergo ovarian hyperstimulation. Patients with lupus may undergo assisted reproduction techniques, including in vitro fertilization (IVF). Ovarian hyperstimulation syndrome (OHSS) is a rare complication of IVF resulting in a capillary leak syndrome; severe OHSS increases risk for thrombosis and renal compromise. Even in a well-controlled cycle, elevated estrogen levels may increase risk of flare and thrombosis in SLE patients. However, thrombosis in aPL-positive patients undergoing IVF is rare, but most reported patients have been treated prophylactically with anticoagulants. Prophylactic anticoagulation may be considered in patients with high-risk aPL profiles and is mandatory for those with confirmed APS. However, aPL antibodies as a cause of failed IVF or infertility is not accepted, and anticoagulation is not indicated to improve IVF cycle outcome [2, 3].

5. Preconception orientation

Good information to the patients and pregnancy planning is essential for a woman with SLE who wants a child. Pregnancy planning is a key point for women

Preconception visit checklist	**Contraindications to pregnancy**
Age	Severe lupus flares within the previous 6 months
Any previous pregnancy?	Severe restrictive lung disease (FVC < 1 L)
Previous pregnancy complications?	Heart failure
Presence of severe irreversible damage?	Chronic renal failure (Cr < 30 mg/dL)
Recent or current lupus activity?	Stroke within the previous 6 months
Presence of antiphospholipid antibodies/syndrome?	Previous severe preeclampsia of HELLP syndrome despite therapy with aspirin and heparin
Other chronic medical conditions?	Severe lung hypertension
(Hypertension, diabetes, etc.)	(Estimated systolic PAP > 50 mm Hg or symptomatic)
Previous nephritis or active nephritis	
Current treatment: any forbidden drugs (including cyclophosphamide, methotrexate, mycophenolate, thalidomide, or thalidomide lyks, angiotensin-converting, enzyme inhibitors, angiotensin II receptor blockers, diuretics, and statins)	
Positive anti-Ro and anti-La	
Anti-DNA, complement levels C3 and C4	

Abbreviations: PAP, pulmonary arterial pressure; FVC, forced vital capacity.

Table 1.
Preconception visit checklist and contraindications to pregnancy in women with SLE.

with SLE. Postponing conception until the disease is inactive for at least the previous 6 months significantly improves the results. Women with irreversible lesions in vital organs are more likely to suffer maternal-fetal morbidity and mortality during and after pregnancy. The pregnancy should be delayed, such as a severe disease flare in the previous 6 months, a recent stroke, and active lupus nephritis. In some situations, pregnancy may be contraindicated (**Table 1**). A profile of autoantibodies, such as aPL (anticardiolipin, anti-β2 glycoprotein I, and lupus anticoagulant), serum levels of complement, anti-SSA, and anti-SSB antibodies [4], is essential as risk factors for complications during pregnancy. Keeping the SLE inactive and the function of organs with safe medications during pregnancy should be a goal. There is an increased risk of complications among women with severe impairment of organ function, with or without serious pre-existing damage. The care of pregnant women with SLE must focus on three mainstays: a coordinated medical-obstetrical care, a well-defined management protocol, and a well-structured prenatal follow-up.

6. Laboratory evaluation during prenatal care

In pregnancy, it is necessary to perform routine pregnancy testing plus other tests that include a complete blood count, kidney and liver function, and proteins in a 24-hour urine collection (**Table 2**). Complementary studies should include additional tests such as complement study (C3 and C4), aCL, LA, aβ2GPI, anti-DNA, anti-SSA, and anti-SSB antibodies [4]. Evaluate the activity of the disease during the prenatal phase. The hormonal changes during pregnancy cause an alteration of the domain of Th1 to Th2 lymphocytes, and, consequently, it is expected that autoimmune disorders involving the Th2 response, such as SLE, are activated. In general, it is accepted that pregnancy can lead to higher rates of outbreaks of the disease, ranging from 25 to 65%. Skin rashes and musculoskeletal symptoms are less common, while renal and hematological flares are more frequent. The risk of flare seems to be related to the onset of disease activity 6–12 months before conception. There is an increased risk of flares during pregnancy when there is lupus nephritis at conception and even in women with pre-existing nephritis in remission. One study showed an exacerbation rate of 30% of SLE activity during pregnancy or postpartum in women with pre-existing lupus nephritis. It is sometimes difficult to distinguish signs and symptoms related to pregnancy from those due to SLE. Some ambiguous manifestations such as fatigue, headaches, arthralgias, edema, hair loss, palmar and malar erythema, anemia, and thrombocytopenia can be confused with clinical manifestations of SLE. An evaluation by physicians experienced in pregnant women with SLE is important. Blood tests with basal blood counts and urinalysis with measurement of proteinuria are useful to control the state of the disease and identify the flare. The production of C3 and C4 increases in the liver during pregnancy, and, therefore, their levels may be within the range of normality in cases of active SLE. Relative variations of complement are more important than absolute levels, and a 25% drop in serum complement levels may suggest a flare of lupus. The determination of the products of complement degradation would be the best way to identify a greater activation. Currently, we have indices to measure the activity of SLE during pregnancy, such as the pregnancy activity index of systemic lupus erythematosus (SLEPDAI) and the index of lupus activity in pregnancy (LAI-P). In practice, the clinical judgment of an experienced clinician is still considered the gold standard, and these indices are essential for publications on SLE and pregnancy. The SLEPDAI scale is an instrument similar to the SLE disease activity index (SLEDAI) to evaluate the activity of lupus, assigning different scores for the

Prepregnancy	Every 6–8 weeks[1]
Complete blood count with platelets	Complete blood count with platelets
Comprehensive metabolic panel	Comprehensive metabolic panel
Prothrombin time/partial thromboplastin tine	Urinalysis with microscopy
Urinalysis with microscopy	Spot protein/creatinine ratio
24-hour urine protein and creatinine clearance[2]	Anti-dsDNA
Spot protein/creatinine ratio	Complement levels (C3, C4)
Anti-dsDNA	Uric acid
Anti-Ro/SSA and anti-La/SSB antibodies	sFlt-1/PlGF ratio (>20 weeks)
Lupus anticoagulant[3]	
Anticardiolipin IgG, IgM[3]	
Anti-β2 glycoprotein I IgG, IgM[3]	
Complement levels (C3, C4)	
Uric acid	

[1] *Adjust interval of monitoring based on clinical situation.*

[2] *In patients with proteinuria, consider repeating 24-hour urine test each trimester.*

[3] *If positive for first time, repeat in 12 weeks.*

Table 2.
Systemic lupus erythematosus pregnancy evaluation and monitoring.

various clinical and laboratory manifestations of lupus activity, however, taking into account the changes, physiological factors of pregnancy, and main pathologies of the pregnancy-puerperal cycle that can simulate an active SLE. The risk of hypertensive disorders during pregnancy increases in the context of active lupus nephritis. The frequency of preeclampsia varies from 7.5 to 22.5% for all women with SLE. Renal involvement of lupus is often associated with hypertension, and the diagnosis of preeclampsia is difficult because it may coincide with chronic hypertension exacerbated during pregnancy. Likewise, in the case of women with SLE with residual glomerular lesions, an increase in proteinuria can be observed, due to the increase in the glomerular filtration rate during pregnancy, and this fact is not related to preeclampsia. The diagnosis of preeclampsia may be more difficult due to the increase in blood pressure and previous proteinuria. The differential diagnosis of preeclampsia in patients with lupus may be facilitated by changes in the C3, C4, and CH50 measurements, since a reduction in these levels is expected during lupus activity. Other laboratory tests are useful to perform a differential diagnosis, such as an abnormal urinary sediment, erythrocytic dysmorphia or cell casts, and increased titers of anti-DNA antibodies (common in lupus nephritis). SLE of onset during pregnancy should be considered as an active lupus and may be associated with a worse outcome of pregnancy. Differentiating preeclampsia into an early SLE during pregnancy is a challenge and often delays the diagnosis of SLE. Among patients with stable SLE at the time of conception, it is expected that the activity of the disease does not worsen, and even if so, the flare is usually mild and involves some type of treatment modification.

7. Evaluation of fetal growth and vitality

Fetal complications are frequent in patients with SLE. Miscarriages and intrauterine fetal death can occur in 20% of pregnancies in patients with SLE. Patients

with a history of nephritis have a higher risk of such adverse outcomes. The rate of restriction of fetal growth (FGR) is close to 30%, even in mild disease, with an increased risk if there is renal involvement. Several studies concluded that the result of the mortality rate for women with SLE tends to be higher, a condition strongly associated with the presence of flares of the disease during pregnancy. Serial obstetric ultrasound is the most important method to guide the monitoring of fetal growth. The measurement of the length of the cranial crown in the first trimester is presented as the most accurate measurement. At 16–22 weeks of gestation, an anatomical survey should be followed that considers the diagnosis of fetal anomalies, which also allows the first growth monitoring. In each 4-week period, new scans must be performed, measuring the volume of amniotic fluid. If preeclampsia is diagnosed, the interval should be reduced. The monitoring of fetal vitality is an important part of the prenatal care of patients with SLE. This should include the nonstress test (NST), the biophysical profile (BPP), and the Doppler velocimetry of the fetal umbilical artery, beginning at 26–28 weeks and continuing weekly until birth. In patients with SLE, alterations of the umbilical artery Doppler velocimetry should be handled in a similar way to those without the condition. The normal evaluation of these tests has a high negative predictive value for fetal death. A relationship exists between abnormal uterine artery Doppler and posterior fetal loss, preeclampsia, FGR, and preterm birth. For women with anti-SSA/anti-SSB antibodies, fetal echocardiography should be performed between 18 and 26 weeks to exclude congenital heart blockage of the fetus. An urgent referral to a tertiary care center should be requested in case of abnormal fetal heart rate, mainly a low heart rate.

8. Recommended SLE treatment during pregnancy

An active SLE is harmful to the mother and the fetus, and an appropriate reflection is necessary between the risks and benefits of the indicated treatment. In practice, it is common for women with SLE to interrupt their medication before conception, for fear of fetotoxicity, which happens through medical advice and proper planning [5]. Stopping the medication can lead to an active SLE and unfavorable pregnancy outcomes. Immunosuppressive treatment in pregnant women with quiescent lupus should not be changed unless it induces fetal malformations. The glucocorticoids and antimalarials are the drugs most used in the treatment of lupus and should be maintained at the same doses during pregnancy. Prednisone at a dose of 5–10 mg/day is considered safe and sustainable during pregnancy. The mild flare of the disease can be treated with low doses of prednisone (less than 20 mg/day), and higher doses of corticosteroids, such as intravenous pulses, will be indicated to treat moderate to severe lupus activity. The antimalarial is not teratogenic and is recommended to prevent the activity of the disease and reduce the risk of cardiac neonatal lupus in patients with anti-Ro antibodies. The use of immunosuppressants is possible during pregnancy, and azathioprine is the safest. Changing other immunosuppressants to azathioprine in a patient with SLE who wants pregnancy is recommended. Some recent report describes leukopenia, thrombocytopenia, and slow development of children exposed to azathioprine during pregnancy. Cyclosporine and tacrolimus, classified as category C by the Federal Drug Association (FDA), are safe during pregnancy initially demonstrated in pregnant women with kidney transplantation. CYC should not be prescribed during the first trimester for causing fetal chromosome, if it can be used during the second or third trimester for severe flares not controlled with pulses of methylprednisolone or other immunosuppressants. The use of CYC during the second and

third trimesters does not seem to increase the risk of congenital anomalies, although spontaneous abortions and premature labor may be more frequent. Treatment with mycophenolate mofetil may be another option during the second and third trimesters, although more experience is lacking. Leflunomide is associated with teratogenic and fetotoxic effects in animals, and its metabolite is detectable in plasma up to 2 years after the interruption. In pregnant women, it is formally contraindicated, and pregnancy should be excluded before starting a treatment with leflunomide. Methotrexate, classified as drug X by the FDA, is teratogenic and produces abortion at high doses; therefore, it is contraindicated in pregnancy. If used in the first trimester, it is associated with FGR and some important malformations, such as absence or hypoplasia of the frontal bones, craniosynostosis, large fontanelle, and ocular hypertelorism. Thalidomide or thalidomide-like is used for the treatment of cutaneous lupus, producing malformations in the fetus, such as phocomelia by thalidomide. Rituximab has a very low transplacental transfer during the first trimester of pregnancy, and some studies of safe pregnancies and deliveries have already been reported in cases of exposure; in the second or third trimester, it can cross the placenta and induce severe neonatal lymphopenia. Therefore, in these cases, live vaccines should be avoided in these children during the first 6 months of life. High blood pressure is a common condition among patients with lupus nephritis; an adequate treatment of blood pressure during pregnancy can reduce the progression of the disease and avoid several adverse pregnancy outcomes. The labetalol, nifedipine, hydralazine, and methyldopa are safe medications to treat hypertension in pregnant women. Angiotensin-converting enzyme (ACE) inhibitors should be avoided due to their association with multiple congenital anomalies. A low dose of aspirin is recommended, since it reduces the risk of preeclampsia and perinatal death; In addition, it is associated with an increase in birth weight in those cases with risk factors, including kidney disease. Complete anticoagulation with low molecular weight heparin (LMWH) is recommended if there has been a previous thrombotic event. Calcium supplements are required, mainly for those women who use corticosteroids and heparin. Also, vitamin D supplements can be given, but it does not reduce unfavorable obstetric risks.

9. Lupus flare management during pregnancy

Many physiological changes in pregnancy can overlap with the characteristics of active disease, which makes differentiation difficult (**Table 3**). Some common laboratory tests also become less reliable: mild anemia and thrombocytopenia are common, the erythrocyte sedimentation rate (ESR) increases, and up to 300 mg/day proteinuria can occur during normal pregnancy. Complement levels increase by 10–50% during normal pregnancy and may appear to remain in the "normal" range, despite the activity of the disease. Anti-DNA antibodies may be useful in the evaluation of disease activity. The scales of activity of the specific disease of pregnancy, the activity index of pregnancy SLE (SLEPDAI), the LAI-P, and the BILAG2004-Pregnancy index have been developed with modifications in the descriptors. A combination of laboratory parameters along with clinical judgment may be the best tool to evaluate the activity of the disease. Based on the numerous risks associated with pregnancy, it is recommended that women with SLE have a preconception assessment and multidisciplinary management with maternal-fetal drugs and rheumatology during pregnancy. Active SLE at the time of conception is a predictor of adverse outcomes. It is suggested that the disease remain inactive for 6 months before attempting pregnancy. Laboratory tests should include, at a minimum, antiphospholipid antibodies (LA, IgG and IgM aCL, IgG, and

	Pregnancy changes	SLE activity
Clinical features	Facial flush	Photosensitive rash
	Palmar erythema	Oral or nasal ulcers
	Arthralgias	Inflammatory arthritis
	Fatigue	Fatigue, lethargy
	Mild edema	Moderate to severe edema
	Mild resting dyspnea	Pleuritis, pericarditis
Laboratory features	Mild anemia	Immune hemolytic anemia
	Mild thrombocytopenia	Thrombocytopenia
		Leukopenia, lymphopenia
	Mild increased ESR	Increased inflammatory marker levels
	Physiologic proteinuria	Proteinuria > 300 mg/day
		Active urinary sediment

Abbreviation: ESR, erythrocyte sedimentation rate.

Table 3.
Overlapping features of pregnancy and systemic lupus erythematosus (SLE).

IgM anti-aβ2GPI I antibodies), anti-Ro/SSA and anti-La/SSB antibodies, and an evaluation of renal function (creatinine, protein/creatinine ratio in urine). Women who have anti-Ro/SSA and anti-La/SSB antibodies should have intensive fetal monitoring for cardiac arrest with fetal echocardiography by weekly pulsed Doppler (to measure the mechanical PR interval) beginning at 16–18 weeks and continuing up to 26–28 weeks of pregnancy. Ideally, all women with SLE should receive HCQ and low doses of aspirin during pregnancy, unless contraindicated. Women who continue HCQ during pregnancy have fewer outbreaks of disease and better outcomes as well as mothers with positive anti-Ro/SSA and anti-LA/SSB antibodies. Low-dose aspirin initiated at 12–16 weeks of gestation reduces the risk of preeclampsia and fetal growth restriction [6]. The interruption of medications used to control the activity of the disease increases the risk of flares and complications associated with pregnancy. Serial ultrasound exams should be performed to assess fetal growth and fetal monitoring before delivery should begin in the third trimester. Renal involvement is common in patients with SLE and may be suspected in the presence of proteinuria or elevated serum creatinine. Hypertension and nephrotic syndrome consist of intense proteinuria, hypoalbuminemia, and peripheral edema, and patients have characteristically low levels of complement (C3) and high levels of anti-DNA. The involvement of the renal vasculature in cases of lupus nephritis is a sign of poor prognosis. In thrombotic microangiopathy, damage to the endothelial cells of small arterioles and capillaries results in thrombosis and mortality. Neuropsychiatric symptoms observed should be considered and excluded, including electrolyte abnormalities, infection, renal failure, and the effects of drugs. In the absence of a standard gold diagnostic test, this can represent a significant clinical challenge, especially in pregnancy and the postpartum period, where specific conditions of pregnancy, such as preeclampsia and eclampsia, can produce the same symptoms. The APS is an autoimmune disorder characterized by vascular thrombosis and/or pregnancy morbidity in the presence of persistent antiphospholipid antibodies. A small subset of patients with APS (<1%) develops multiple organ failure secondary to a disseminated thrombotic disease, a condition called catastrophic APS (CAPS) that has a mortality rate of up to 50%.

The treatment of flares during pregnancy is guided by the severity and involvement of the organ, similar to the state of nonpregnancy. However, the choice of agents is limited to safe medications, as discussed above. The steroids should be used in the lowest possible doses, but short cycles of high doses can be used for flare control. NSAIDs can produce malformations, and in general their indication in the SLE is in disuse. The antimalarial should be continued throughout pregnancy. Azathioprine and anti-calcineurin can occur throughout pregnancy. Azathioprine is a safe immunosuppressant with much experience in pregnancy, although delays in the development of the offspring have recently been reported. IVIg and plasmapheresis are still alternative options, but the increased risk of thrombosis with IVIg and fluid overload should be considered, although it is rarely necessary if we exclude intravenous Ig treatment of severe thrombocytopenia in pregnancy. Physiological changes in pregnancy such as an increase in glomerular filtration rate and renal plasma flow can worsen pre-existing kidney disease. However, in theory, a rapid decrease in the levels of the pregnancy hormone, particularly estrogen, may be advantageous. It is known that the immunosuppressive drugs used to treat SLE, such as CYC, cross the placenta and have teratogenic effects. In addition, this particular medication has been associated with premature and irreversible ovarian failure.

10. Lupus pregnancy, nephritis, and eclampsia

Lupus nephritis is an important risk factor for both maternal and fetal complications. A meta-analysis of 37 studies from 1980 to 2009 included 2751 pregnancies with SLE: the SLE flare rate was 25.6%, and the rates of preterm birth and IUGR were 39.4 and 12.7%, respectively. Positive associations were identified between preterm birth and active nephritis, hypertension and active nephritis, and preeclampsia and history of nephritis [7]. Up to 25% of women with SLE will develop preeclampsia compared to 5% in the general population. Doctors who treat lupus and pregnancy should ask themselves questions like does the presence of increased proteinuria and hypertension represent a flare or does the presence of increased proteinuria and hypertension represent the onset of preeclampsia? At the beginning of pregnancy, the presence of new or worsening proteinuria and hypertension will almost always represent a flare of lupus nephritis. However, beyond 20 weeks of gestation, differentiating a flare of preeclampsia poses a diagnostic as well as a therapeutic challenge (**Table 4**). Flare of lupus nephritis in pregnancy may be the first presentation of lupus and is relatively rare in those without previous nephritis or inactive nephritis at the beginning of pregnancy. However, if a woman has proteinuria, hypertension, renal function decreased at the beginning of pregnancy, and a history of lupus nephritis, she is likely to have a flare of lupus nephritis. The clinical history plus appropriate biochemical investigations is key to the diagnosis of clinical complications in SLE and pregnancy. The complement should be normal or high in pregnancy because it behaves as an acute phase reactant since this is pregnancy. The decrease in complement, even within the normal range, should alert us to a possible flare of SLE and more when associated with an increase in anti-dsDNA. If proteinuria is significant and unexpected, it can mean a change in immunosuppression and even renal biopsy if the woman is in the first trimester or in part during the second trimester, although it is only necessary if the clinic and laboratory are discordant. Always keep in mind if the woman is at risk of bleeding after the biopsy and for how long anticoagulation can be delayed in a pregnant woman with intense proteinuria and possibly phospholipid antibodies who, therefore, have a high risk of thrombovenous embolism, since the procoagulant

Clinical measure	Preeclampsia	Lupus nephritis
Time	>20 weeks	>20 weeks
Hypertension	Present	Often present
Urine active sediment	Rare	Common
Onset of proteinuria	Abrupt, after 20 weeks	Abrupt or gradual, anytime
Uric acid	>4.9 mg/dl	<4.9 mg/dl
C3 and C4	Usually normal	Usually low or decreasing
Complement products	Normal	Usually higher
Anti-DNA	Negative or stable	Positive or increasing
Lupus activity	No	Yes
Urine calcium	<195 mg/day	>195 mg/day
Thrombocytopenia	Yes (HELLP)	20% of SLE
Liver function test	May be elevated (HELLP)	Usually normal
Kidney biopsy	Glomeruloendotheliosis	SLE nephritis
sFlt-1/PlGF ratio	Higher	Normal

Abbreviations: HELLP, hemolysis, elevated liver enzymes, and low platelets; SLE, systemic lupus erythematosus; sFlt-1, soluble fms-like tyrosine kinase; PlGF, placental growth factor.

Table 4.
Differentiation of preeclampsia from lupus nephritis flare in pregnancy.

factors are added, pregnancy, nephropathy, SLE activity, and/or aPL. If the risk of having thromboembolism outweighs the benefit of a firm diagnosis, a biopsy should not be done. However, if there is a biochemistry compatible with a flare of lupus, patient's history contains nephritis flares and it is seems that it is going to be repeated; a kidney biopsy could be justified. The distinction of nephritis from lupus of pregnancy preeclampsia (from 26/40 weeks of gestation) can be difficult. In both, there will be an increase in proteinuria, hypertension, generalized symptoms, thrombocytopenia, and kidney damage. In women with isolated preeclampsia, there should be no hematuria, urinary cylinders, a decreasing complement, or increasing anti-dsDNA. However, a flare of lupus nephritis increases the risk of preeclampsia, so, again, distinguishing the two can be a challenge for the clinician. The two treatments are different; preeclampsia requires delivery sooner rather than later, and lupus nephritis requires immunosuppressive treatment. It is not yet a usual practice, but it is likely to be exceptionally useful, measuring angiogenic and antiangiogenic factors, to determine if there is preeclampsia present. Women with APS and SLE who developed preeclampsia had a median of sFlt-1 (tyrosine kinase similar to soluble fms), low placental growth levels (PIGF), and a significantly higher sFlt-1/PlGF ratio, and significantly higher PIGF levels lower compared with women with APS and SLE and without preeclampsia after 12 weeks of gestation. These differences increased with gestational age. The sFlt-1/PlGF ratio became a significant predictor of preeclampsia at 12 weeks, showing the highest levels at 20, 24, and 28 weeks of gestation [8, 9]. Later, the fall of the placental growth factor predicted the appearance of preeclampsia even in women with pre-existing chronic kidney disease. A recent publication highlights the evidence (or more commonly the lack of evidence) for the best use of antirheumatic drugs before and during pregnancy. Women who take azathioprine, hydroxychloroquine, cyclosporine, and tacrolimus can safely breastfeed their babies, so women who take these medications should not be discouraged from breastfeeding.

There are still no safety data on the MMF, so breastfeeding is discouraged if MMF is required. The woman with SLE and pregnancy should be treated as high-risk. At the controls ask for symptoms of the disease to detect SLE flare, and always check the blood pressure to detect preeclampsia. A blood and urine test should be done every quarter to detect biological changes in the complement and anti-DNA that suggest a flare. The fetus must be carefully monitored to detect growth and blood flow. Good multidisciplinary coordination among obstetrician, nephrologists, rheumatologists, and nursing experts is essential for better results.

11. Pregnancy and antiphospholipid antibodies

Pregnancy in women with SLE and aPL-positive courses with obstetric is 80% of cases. The current standard treatment for patients with obstetric includes LDA (75–100 mg/day) and low molecular weight heparin (subcutaneous enoxaparin, dalteparin, nadroparin, or subcutaneous tinzaparin) or unfractionated heparin. These recommendations are based on the results of randomized controlled trials comparing LDA alone or in combination with heparin with APS [7]. Kutteh et al. reported a significant improvement in the rate of live births with LDA and heparin versus LDA alone (80 versus 44%, $P < 0.05$). Rai et al. showed a significantly higher rate of live births with LDA and unfractionated heparin (5000 units) versus LDA alone (71 versus 42%, OR, 3.37, 95% CI, 1.40–8.10). However, no differences were found in the results with the combined treatment versus the LDA in two other randomized trials, both with LMWH, with live birth rates close to 80% in both groups. The heterogeneity in the findings seems to be attributed to the relatively poor results in women who received LDA alone in the two previous studies. In addition, data from observational studies have reported pregnancy success rates of 79–100% with LDA alone in this subgroup of women, although many of these cases had low levels of aPL antibodies. The current recommendation for the treatment of obstetric APS is to initiate LDA plus LMWH at therapeutic doses.

All women should be evaluated for risk factors for venous thromboembolism and should receive postpartum thromboprophylaxis. The Royal College of Gynecology in the United Kingdom, for example, recommends, for aPL-positive women without clinical manifestations of APS, 7 days after thromboprophylaxis of labor, and for women with APS, this extends to 6 weeks. All women with APS can deliver natural light, unless there are obstetric reasons to suggest otherwise. In addition, all women should be encouraged to stop smoking and reduce/discontinue alcohol consumption in accordance with the national pregnancy guidelines. Patients with a recent thrombotic event in the last 3 months, particularly high blood pressure and/or uncontrolled, should be encouraged to postpone new pregnancies. Patients with pulmonary hypertension in general are advised not to get pregnant. Women with previous thrombosis should receive long-term anticoagulation once the risk of postpartum hemorrhage has stabilized. Both AVK (antivitamin K) and heparins are compatible with breastfeeding. With respect to fetal monitoring during pregnancy, the bilateral uterine notch between 23 and 25 weeks of gestation has been shown to be an independent risk factor for the development of early-onset preeclampsia and gestational hypertension. Therefore, the bilateral notch of the uterine artery should be considered in the risk assessment for the development of these pregnancy complications. The evaluation of thrombotic risk should also be considered in patients with a history of obstetric primary health center. Among others, Lefevre et al. demonstrated that patients with obstetric APS have a higher thrombotic risk compared to healthy women (3.3 versus 0–0.5/100 patient years), even if treated with LDA. Similarly, in a 10-year observational study of 1592 women

with pure obstetric SAP and no history of thrombosis, Gris et al. demonstrated that the LA was a risk factor for superficial and superficial venous thrombosis and unprovoked distal and similar results have been demonstrated in other studies.

The current treatment to prevent obstetric morbidity in primary health center (PHC) has improved the outcome of pregnancy at a rate of live births of more than 70%. Given that 30% of women continue to have complications during pregnancy, international groups are currently evaluating different options to improve pregnancy outcomes in women with APS. The additional use of low doses of steroids has been evaluated in refractory APS. It has been suggested that intravenous immunoglobulin improves pregnancy complications in obstetric PHC. Treatment with pravastatin suggests a beneficial role in those women with preeclampsia related to established aPL. In their case series, 11 patients are treated with pravastatin 20 mg/day in addition to the standard treatment, while the controls continued alone with LDA and LMWH. In all patients exposed to pravastatin, signs of preeclampsia, such as blood pressure and proteinuria, improved and signs of placental perfusion remained stable without further deterioration compared to the control group. HCQ has also been evaluated. The HCQ immunomodulator can have beneficial effects not only in the treatment of thrombotic APS but also in the prevention of pregnancy complications [10]. The European randomized controlled multicenter trial "HYPATIA" will evaluate the role of HCQ versus placebo in pregnant women with aPL and, hopefully, provide stronger evidence on the use of HCQ in this context. Complement activation, and therefore a potential role for eculizumab, has also been introduced as a potential target for therapy with APS. The participation of complement activation was investigated for the first time in murine models of pregnancy morbidities related to aPL, and increasing evidence is emerging from both in vitro and in vivo studies. The complement can be activated by binding of the C3 fragment to the Fc receptor of aPL antibodies or by the formation of autoantibodies against C1q, which are frequently detected in patients with APS. The activation of the complement pathway and, consequently, the production of inflammatory molecules such as C5a by aPL, can directly activate platelets and monocytes, inducing the coagulation cascade, which leads to the clinical manifestations of APS. Although in the current literature several case reports describe the successful use of eculizumab in severe cases of APS, such as catastrophic antiphospholipid syndrome (CAPS) and cases of APS and thrombotic microangiopathy, the potential role of eculizumab should be further investigated.

12. Neonatal lupus

Pregnancies in women with anti-Ro and anti-La have an increased risk of developing neonatal lupus (NLS) with or without lupus. Maternal antibodies cross the placental barrier giving a passively acquired fetal autoimmunity. Cutaneous lesions of subacute lupus and hematologic and/or hepatic alterations of the NLS tend to resolve with the elimination of maternal antibodies from 6 to 8 months of age, but the lesion of the developing fetal cardiac conduction pathway can be irreversible. Cardiac injuries include conduction defects, structural abnormalities, cardiomyopathy, and congestive heart failure, but the most serious complication is the development of irreversible complete heart block (CHB), which is associated with a high fetal mortality of 20%. NLS can affect 2% of pregnancies exposed to anti-Ro, but recurrence rates in new pregnancies are 16–20% after a first NLS event. The majority (up to 70%) of the survivors require the insertion of a permanent pacemaker and periodic changes of the same as the child will grow. The CHB may be preceded by lower degrees of driving delays, although it may be sudden onset. Most of the events

occur between 18 and 24 weeks of gestation, but there are later cases, and even postpartum CHB has been described. Early detection and initiation of treatment could stop progression to CHB, but reversal of established CHB has not been reported. Multiple monitoring tools have been proposed for the early detection of cardiac conduction disorder, but fetal Doppler echocardiography remains the most widely used method. The most vulnerable period is between 18 and 24 weeks of pregnancy, so it is recommended in this period of pregnancy to monitor weekly all exposed fetuses, and then every 2 weeks. The detection of an early conduction defect with a prolonged RP interval should indicate the start of a prophylactic treatment to avoid CHB, although we do not have any effective guidelines. The maternal administration of fluorinated corticosteroids and beta-agonists has shown benefits in some specific cases. The treatment of established CHB remains an unresolved problem with minimal benefit with any available approach. The high risk of recurrence in subsequent pregnancies justifies prophylactic therapy for pregnancies at risk. The beneficial effects of IVIg were reported in open studies, but two randomized controlled trials were negative. Both trials have been criticized for their methodology, but the use of IVIg in this context can still be considered as an option. HCQ again deserves special mention. Several studies have shown that HCQ reduces the risk of cardiac NLS in fetuses at risk and possible recurrences. In view of the multiple beneficial effects of HCQ, it is indicated in all pregnant women with lupus and anti-Ro [11].

13. Delivery

Women with SLE have an increased risk of preterm birth. This can occur spontaneously or due to maternal and/or fetal complications, such as a flare of severe lupus, preeclampsia, and FGR. Between 24 and 34 weeks of gestation, the acceleration of fetal lung maturation is essential, with steroids (preferably betamethasone), regardless of any steroid administered previously. Magnesium sulfate when gestational age is <32 weeks, due to its neuroprotective benefits for the fetus, should be administered in cases of severe preeclampsia. The objective in a pregnant patient with SLE should be a spontaneous delivery at term via the vagina. However, available data have revealed that women with SLE undergo a higher cesarean section (>33%, odds ratio (OR) 1.7, confidence interval (CI) 95% 1.6–1.9). Despite this, it is recommended that cesarean sections be reserved only for obstetric indications, due to their additional risk factor for venous thromboembolism (VTE), blood loss and infection, and repercussions for future pregnancies. Intravenous hydrocortisone may be necessary to overcome the physiological stress of labor if long-term oral steroids, which are very common in SLE, have been taken. The standard prophylactic LMWH should be discontinued at the start of spontaneous delivery and the night before induced labor or elective cesarean section. Regional anesthesia (epidural or spinal) can be performed 12 hours after the last dose of LMWH.

14. Postpartum care

In the puerperium, we must control the activity of the SLE for the detection of flare or coexisting preeclampsia. The treatment for postpartum active SLE is similar to that of nonpregnant women. However, the use of some drugs may have effects on the nursing infant. Therefore, the risks and benefits of continuing to breastfeed should be clarified to the nursing mother. All women who received antenatal LMWH should continue using it for 6 weeks after delivery, in a prophylactic dose, since the puerperium is also a period of increased risk of VTE. In patients with

SLE, postpartum advice to offer safe contraception is particularly important. Good options are long-acting reversible contraception methods. The use of progestogens is only safe and can become an appropriate option. Contraceptives containing estrogen will not use women with aPL or APS, SLE with moderate to severe flare, lupus nephritis, and some other conditions, such as hypertension, smoking, obesity, or previous VTE, since they increase the risk of VTE. In cases of well-defined SLE with stable and/or mild disease, the use of combined oral contraceptives may be indicated. Contraceptive barrier methods have a high failure rate (15–32%) and, therefore, should not be used as a single method.

Abbreviations

SLE	systemic lupus erythematosus
LA	lupus anticoagulant
aCL	anticardiolipin antibody
aβ2GPI	anti-β2 glycoprotein I
aPL	antiphospholipid antibody
HELLP	hemolysis, elevated liver enzymes, and low platelets
sFlt-1	soluble fms-like tyrosine kinase
PlGF	placental growth factor
CYC	cyclophosphamide
LMWH	low molecular weight heparin
ESR	erythrocyte sedimentation ratio
MMF	mycophenolate mofetil
HPA	hypothalamic pituitary axis
AMH	anti-mulleriana hormone
GnRH	gonadotrophic hormone receptor
IUDs	intrauterine devices
IVF	in vitro fertilization
OHSS	ovarian hyperstimulation syndrome
SLEPDAI	SLE pregnancy disease activity index
LAI-P	lupus activity index pregnancy
FGR	fetal growth restriction
NSAIDs	nonsteroidal anti-inflammatory drugs
ACE	angiotensin-converting enzyme
DMPA	depot medroxyprogesterone acetate
SLEDAI	SLE disease activity index
PHC	primary health center
FDA	Federal Drug Association

Author details

Jose Ordi-Ros[1*], Cristina Sole Marce[2] and Josefina Cortes-Hernandez[1]

1 Internal Medicine, Vall d'Hebron Hospital, Barcelona, Spain

2 Lupus Research Unit, Vall d'Hebron Research Institute, Barcelona, Spain

*Address all correspondence to: jordi@vhebron.net

IntechOpen

References

[1] Pastore DEA, Costa ML, Parpinelli MA, Surita FG. A critical review on obstetric follow-up of women affected by systemic lupus erythematosus. Revista Brasileira de Ginecologia e Obstetrícia. 2018;**40**:209-224

[2] Bălănescu A, Donisan T, Bălănescu D. An ever-challenging relationship: Lupus and pregnancy. Reumatology. 2017;**55**:29-37

[3] Sammaritano LR. Management of systemic lupus erythematosus during pregnancy. Annual Review of Medicine. 2017;**68**:271-285

[4] Buyon JP, Kim MY, Guerra MM, Laskin CA, Petri M, Lockshin MD, et al. Predictors of pregnancy outcomes in patients with lupus: A cohort study. Annals of Internal Medicine. 2015;**4**:153-163

[5] Lateef A, Petri M. Systemic lupus erythematosus and pregnancy. Rheumatic Diseases Clinics of North America. 2017;**43**:215-226

[6] Eudy AM, Siega-Riz AM, Engel SM, Franceschini N, Howard AG, Clowse MEB, et al. Effect of pregnancy on disease flares in patients with systemic lupus erythematosus. Annals of the Rheumatic Diseases. 2018;**77**:855-860

[7] Moroni G, Ponticelli C. Important considerations in pregnant patients with lupus nephritis. Expert Review of Clinical Immunology. 2018;**14**:489-498

[8] Mayer-Pickel K, Stern C, Eberhard K, Lang U, Obermayer-Pietsch B, Cervar-Zivkovic M. Angiogenic factors in pregnancies of women with antiphospholipid syndrome and systemic lupus erythematosus. Journal of Reproductive Immunology. 2018;**127**:19-23

[9] Kim MY, Guerra MM, Kaplowitz E, Laskin CA, Petri M, Branch DW, et al. Complement activation predicts adverse pregnancy outcome in patients with systemic lupus. Annals of the Rheumatic Diseases. 2018;**77**:549-555

[10] Cortés-Hernández J, Ordi-Ros J, Paredes F, Casellas M, Castillo F, Vilardell-Tarres M. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: A prospective study of 103 pregnancies. Rheumatology (Oxford, England). 2002;**41**:643-650

[11] Abdwani R, Al Shaqsi L, Al-Zakwani I. Neonatal and obstetrical outcomes of pregnancies in systemic lupus erythematosus. Oman Medical Journal. 2018;**33**:15-21

Section 3

Neuropsychiatric Lupus

Chapter 6

Neuropsychiatric SLE: From Immune Mechanisms to Clinical Management

Emily Zhang and Trine N. Jorgensen

Abstract

In this chapter, we will describe neuropsychiatric lupus (NPSLE) as it develops and is treated in lupus patients, as well as means to study the disease using animal models. Based on mouse studies, we will discuss the correlation between inflammatory mediators, such as cytokines and autoantibodies, and the development of neurological symptoms with specific emphasis on the evidence for systemic versus local effects. We will describe specifically the effect of these mediators on the blood-brain barrier, microglia cell function, and the immune system. In addition, we will summarize signs and symptoms in NPSLE patients, especially with respect to primary versus drug-induced neurological issues and current treatment strategies. The chapter will offer a comprehensive review of old and new studies in animal models and patient populations and offer insight into how these results align with current treatment strategies offered to patients.

Keywords: neuropsychiatric lupus, animal models, autoantibodies, cytokines, treatment

1. Introduction

This chapter covers aspects of neuropsychiatric systemic lupus erythematosus (NPSLE), including basic science, as well as clinical features and management. Animal studies have been invaluable in informing our knowledge of pathogenesis and pathophysiology, especially in regard to elucidating immune mechanisms. Studies in two of the most commonly used mouse models, MRL/lpr and (NZB/NZW)F1 (NZB/W), have led to the identification of autoantibodies and cytokines implicated in NPSLE development. Specific antibodies include anti-NMDA-NR2 and anti-ribosomal P antibodies, as well as anti-phospholipid antibodies, that may play a role in perturbing the blood-brain barrier (BBB). There is evidence that BBB permeability may be the second hit needed to induce NPSLE, and cytokines have been repeatedly implicated in this process. Clinical correlations strengthen the argument for autoantibody and cytokine involvement in the pathogenesis, given the discovery of elevated cytokine and autoantibody titers in cerebrospinal fluid (CSF) from patients. Additionally, studies have been performed, whereby autoantibodies identified in NPSLE patients were injected into mouse models to induce an NPSLE phenotype.

Since microglia are the major immune cells of the brain, we separately discuss how their activation can lead to pathophysiology. A connection with estrogen receptors may also exist as seen in MRL/lpr mice. In addition, new evidence suggests that one of the most frequently studied cytokines in SLE, interferon-α (IFNα), may play an important role in NPSLE etiology. As such, studies have shown that deficiency in the IFNα/β receptor can reduce both systemic and neurological diseases in multiple lupus mouse models. Interestingly, IFNα has been independently associated with mood and cognitive symptoms, as seen in the side effects experienced by those who use it as treatment for various cancers and viral infections.

One aspect of NPSLE research that delves more into the clinical realm is the identification of biomarkers. A number of studies have looked at various potential biomarkers, including the aforementioned cytokines and autoantibodies. We review the evidence and emphasize the lack of consistent correlation, which is often a result of the wide ranging, vague, and often subjective manifestations of NPSLE. These include cerebrovascular disease, seizures, myelopathy, aseptic meningitis, movement disorders, and demyelinating syndrome. Psychiatric features have also been described, such as psychosis and mood changes. Some of the more vague symptoms include cognitive dysfunction and acute confusional state. Because these clinical features often overlap with other neuropsychiatric conditions and many of these symptoms are difficult to quantify, reports of epidemiology are highly variable ranging anywhere from a prevalence as low as 12% to as high as 95%. Although NPSLE still often remains a diagnosis of exclusion, we cover consensus case-definition criteria and explore the role, if any, of imaging such as quantitative MRI.

Lastly, we discuss the management of NPSLE, which, due to the complexity in diagnosis and lack of disease activity markers, has been mostly empirical. Corticosteroids and immunomodulators continue to be the mainstays of treatment, although they present numerous side effects. In addition, symptomatic therapy, including anticonvulsants, antidepressants, or antipsychotic medications, can be used. Antiplatelet and anticoagulation therapy should also be considered to manage cerebrovascular risk factors in those with antiphospholipid antibodies. In summary, the body of knowledge about the pathophysiology of NPSLE leaves much to be desired. Further studies in mouse models are necessary to identify more consistent biomarkers and develop targeted treatments for patients suffering from this disease.

2. Animal models used to study neurolupus

Given the difficulties in studying NPSLE in patients due to unclear associations with symptoms and timing of diagnosis, as well as overlap with other neurological and psychiatric syndromes, the use of murine models has been invaluable for elucidation of pathological mechanisms and identification of better therapeutic targets. Three families of murine models for SLE have been studied, including spontaneous models, induced models, and genetically engineered models. Within spontaneous models, typically generated by selective inbreeding, the most commonly used models to study neuropsychiatric manifestations include the F1 hybrid between New Zealand Black (NZB) and New Zealand White (NZW) mice called the (NZB/NZW)F1 hybrid (NZB/W) and the Murphy Roths large (MRL) strain [1]. NPSLE has not been studied extensively in induced or genetically engineered models.

2.1 MRL/lpr mice

The MRL/lpr model carries a spontaneously occurring mutation in the lymphoproliferative (lpr) gene on the MRL inbred background. The lpr mutation is linked to

a variation in the fas gene that causes failure of lymphocytes to undergo apoptosis [2]. The result of this mutation is the accumulation of CD4, CD8, and CD3 T cells in lymphoid tissue [3]. MRL/lpr mice develop an accelerated and aggressive lupus-like disease characterized by immune-mediated damage to the kidneys, skin, heart, lungs, joints, and brain and by the presence of circulating autoantibodies against dsDNA and Smith antigen [1]. Young MRL/lpr mice also spontaneously develop behavioral dysfunction and mood changes, as well as a depressive-like behavior as measured by the forced-swim test [4]. The presence of depressive symptoms in MRL/lpr mice has been found to correlate with titers of autoantibodies against dsDNA, the NMDA receptor, and cardiolipin [4]. Additionally, MRL/lpr mice display loss of preference for sweetened fluids, reflecting anhedonia, which is a core feature of major depression in humans [5].

Brain growth appears to be stunted in MRL/lpr mice, and ventricles increase in size along with development of autoimmune manifestations [1, 6]. More specifically, increased neurodegeneration, reduced dendritic complexity, and progressive atrophy of pyramidal neurons have been seen in the hippocampi of MRL/lpr mice [1]. Cyclophosphamide immunosuppression prevented atrophy and increased dendritic branching in MRL/lpr, thereby supporting the notion that autoimmunity is at least partly responsible for decreased brain growth possibly also affecting behavioral alterations [7].

Finally, SLE in humans has a well-known sex bias affecting females 9–10 times more than males [8]. Interestingly, this bias seems to be recapitulated in the depressive phenotype and autoantibody titers of MRL/lpr mice, with females exhibiting accelerated signs of both depression and autoantibodies as early as 5 weeks as compared to 18 weeks in males [9]. This suggests that autoantibodies may be implicated in the pathogenesis of NPSLE phenotype in this mouse model, as will be discussed further below.

2.2 (NZB/NZW)F1 mice

The NZB/W model develops a spontaneous and severe autoimmune disease with autoantibodies and defective immune complex clearance [10]. Manifestations of lupus in the NZB/W model resemble those of MRL/lpr mice. While they do not develop lymph node hyperplasia, they succumb to a progressive glomerulonephritis leading to fatal renal failure [2]. The sex bias of SLE is also recapitulated in NZB/W mice, with female mice exhibiting accelerated disease [11]. Beneficial effects from treatment with antiestrogen agent tamoxifen suggest that the sex difference is at least partly due to estrogen [12]. Signs of neurolupus in NZB/W mice manifest as progressively increasing anxiety behavior and decreasing exploratory behavior [13], as well as learning and memory deficits that develop later in the disease course [14]. Moreover, immunosuppressive treatment with cyclophosphamide and prednisolone alleviated behavioral deficits in this mouse model [15]. Brains of NZB/W mice have mononuclear infiltration of cerebral and hippocampal blood vessels and in the choroid plexus [14]. Moreover, the mice display a reduction in neuropeptides, namely neuropeptide Y, substance P, and calcitonin gene-related peptide P in the cortex, hippocampus, and hypothalamus that correlate with the development of neurological deficits [16]. It was in this mouse model that anti-dsDNA antibodies were found to be cross-reactive with a peptide sequence, which was also found in humans and later identified to be a subunit of a neurotransmitter receptor (NMDAR-NR2) [17, 18], as addressed below.

3. Understanding of NPSLE-like pathogenesis

Polyclonal B cell activation and autoantibody production seem to play a major role in the pathogenesis of SLE; however, the initial events leading to this activation

and deregulation remain undetermined [2]. Still, overwhelming evidence supports a pathogenic role for autoantibodies as will be discussed further below.

One consideration necessary when discussing NPSLE pathogenesis, however, is how antibodies produced subsequent to B cell activation gain access to the CNS. The brain is immunoprivileged due to the existence of multiple barriers regulating entry of immune cells and compounds such as antibodies. As a result, it has long been thought that some kinds of disruption in these barriers are necessary for NPSLE disease to manifest [19]. This notion is further supported by the observation that some SLE patients have brain reactive autoantibodies in their sera but do not have neuropsychiatric disease [20, 21].

3.1 Three types of barriers

In addition to a high metabolic demand, the brain requires a tightly regulated environment free of toxins and pathogens, which is maintained by three types of barriers: the blood-brain barrier (BBB), the meningeal barrier in the arachnoid matter, and the blood-cerebrospinal-fluid-barrier (BCSFB) [19]. Due to the paucity of data in the literature, the meningeal barrier will not be further discussed here.

The BBB is perhaps the most widely discussed of the three, as it protects the brain from toxic elements in the blood but also allows for the entry and exit of compounds in a finely controlled manner [19]. This balance is achieved via coordination between multiple cell types that are collectively known as the neurovascular unit (NVU) [22–24]. The NVU consists of endothelial cells lining the capillaries, neurons, astrocytes, pericytes, and microglia [22]. Tight junctions between endothelial cells form a layer on the luminal side of capillaries, thereby restricting paracellular diffusion. Pericytes are embedded in the basal lamina matrix that surrounds endothelial cells, and astrocyte endfeet reside on the outer surface of the basal lamina [22]. Astrocytes are thus able to communicate with both vasculature, as well as local neurons. Finally, resident microglia use long processes to survey the microenvironment near the NVU [22].

The BCSFB separates the blood from the ventricular system, which is comprised of the lateral, CSF-filled third and fourth ventricles. CSF is produced and secreted by the choroid plexus, which consists of cuboidal epithelium that, among other characteristics, contains transporters that regulate CSF composition [25]. Albumin quotient and IgG index in the CSF are commonly used surrogates for BBB disruption; however, it should be noted that it is difficult to distinguish whether the source of these molecules is from BBB or BCSFB disruption, and further studies are needed to determine the relative importance of these barriers [19].

Historically, studies in mice have suggested that there need to be a "second hit," namely a breach in the BBB for antibodies to access the brain, however, was recently challenged by studies failing to find an effect of BBB disruption [26], but rather an impact of BCSFB disruption [27]. As such, using exogenous tracers, Gelb et al. failed to find significant changes in BBB permeability in MRL/lpr mice but found abnormal function of the BCSFB in the choroid plexus, a potential site for lymphocyte infiltration [27]. Further studies are needed to identify the relative significance of BBB and/or BCSFB disruption in different animal models and in response to different inflammatory factors including cytokines and autoantibodies.

3.2 Evidence for BBB permeability

Older MRL/lpr mice have significant elevations of IgG and albumin levels in the CSF, suggestive of BBB disruption [28]. This is further corroborated by studies showing IgG filtration into brain parenchyma in MRL/lpr mice and increased permeability of nonautoimmune endothelial cells on treatment with serum from MRL/lpr mice compared with serum from controls [29]. Interestingly, these effects were

found to be mediated by terminal complement factor C5a [29], although further studies investigating the influence of complement on neurolupus phenotypes in MRL/lpr mice have yet to be performed. Another possible sign of BBB disruption is the finding that CD3 T cells penetrate into the choroid plexus and parenchyma of MRL/lpr mice [30]. Interestingly, the presence of brain infiltrating CD3 T cells was accompanied by splenomegaly and retarded brain growth [30], suggesting leukocyte infiltration as a mechanism for neurodegeneration. Finally, the BBB of MRL/lpr mice has also been found to stain for C1q complement particles and IgG, suggesting the presence of immune complexes [31], although whether such complexes are functional or diagnostic remains to be determined. Finally, it should be mentioned that aquaporin 4 expression was increased in brains of MRL/lpr mice but reduced in response to a soluble complement inhibitor, suggesting that complement may play a specific role in driving cerebral edema and inflammation [31].

3.3 Brain-reactive antibodies

Evidence for the presence and involvement of brain-reactive antibodies (BRA) comes from the finding that levels of CSF IgG correlate with immobility on the forced-swim test in MRL/lpr mice [32]. Specific BRAs have been identified and suggested to play a role in initiating, driving, or propagating NPSLE and will be discussed below.

3.3.1 Anti-NR2 antibodies

Glutamate is the main excitatory neurotransmitter of the brain, and the N-methyl-D-aspartate receptor (NMDAR) is an ionotropic glutamate receptor subtype consisting of two NR1 subunits in a complex with two of the four NR2 (a–d) or two NR3 (a and b) subunits [33]. It was discovered in the early 2000s that a subset of anti-dsDNA antibodies cross-react with the NR2 subunit of the NMDA receptor [34]. Anti-NR2 antibodies have been found in the sera of both NZB/W and MRL/lpr mice and correlate with hippocampal and amygdala neuronal dysfunction and death even before NPSLE symptoms [17, 18, 35]. Neurons in the amygdala, anterior hypothalamus, cerebellum, and the hippocampus express a high density of NMDARs with subunits NR2a and NR2b [36], and so it follows that anti-NR2 antibodies would correspond with cognitive dysfunction. In clinical studies of SLE patients, up to 81% carry the anti-NMDA-NR2 antibodies, and anti-NR2 titers in the CSF of SLE patients correlate with diffuse symptoms, such as cognitive impairment, memory decline, impaired attention or executive functions, and depression [37]. The pathogenicity of anti-NR2 antibodies was further corroborated by the finding that transfer of isolated antibodies from lupus patient serum directly into the brains of nonautoimmune mice-induced neuronal cell death and impaired cognition [38, 39]. Interestingly, the concentration of anti-NR2 autoantibodies affects the function of the NMDA receptor differently; while low concentrations change synaptic function, high concentrations promote excitotoxicity, resulting in neuronal cell death by overactivation of glutamate receptors and excessive calcium influx [40], making quantitative measurements important for diagnosis and treatment. It should be noted that in these studies, pharmacological breach of the BBB was necessary for symptoms to occur and only achieved with intravenous administration of lipopolysaccharide or epinephrine, eliciting a strong cytokine response driving BBB disruption.

3.3.2 Antiribosomal P antibodies

In the late 1980s, an association was found between elevated serum titers of antiribosomal protein (RP) antibodies and lupus psychosis in NPSLE patients [41].

Although subsequent studies continued to find an association, an international meta-analysis subsequently found that anti-RP antibodies had limited diagnostic value [20]. Still, when anti-RP antibodies from NPSLE patients were injected into the ventricles of mice, animals developed depressive-like symptoms as measured by immobility [42]. Brains of these mice also showed anti-RP antibody staining in the hippocampus, cingulate cortex, and the primary olfactory piriform cortex [42]. Interestingly, symptoms were partially reversed when a specific anti-idiotypic antibody to anti-RP was administered [42]. Additionally, one study found that human-derived anti-RP antibodies affected glutamatergic synaptic transmission and plasticity related to memory in the hippocampus [43]. These findings are supported by studies showing an association between depression and the presence of anti-RP antibodies in lupus patients [44–46].

3.3.3 Antiphospholipid antibodies

Antiphospholipid syndrome (APS) is defined by the presence of lupus anticoagulant (LA) or anti-β2-glycoprotein-I (β2-GPI), which is a subset of anticardiolipin (aCL) antibodies. SLE patients with APS are more likely to develop infarcts, stenotic arterial lesions, and white matter hypertrophy compared with SLE patients without APS [47]. Antiphospholipid antibodies have also been associated with psychosis in one [48] but not another [49]. Still, a meta-analysis of autoantibodies present in NPSLE patients found an increased prevalence of antiphospholipid (APL) positivity in patients with cerebrovascular disease and cognitive dysfunction [50].

A similar correlation was found in animal models. Mice immunized with a pathogenic monoclonal aCL antibody developed hyperactive behavior in an open field, and examination of brain tissue revealed thrombotic capillary occlusion and mild inflammation [51]. To further explore aCL antibody pathogenicity, Ig from an APS patient was administered into the ventricles of mice and was subsequently found to bind to the hippocampus and cerebral cortex [52]. The level of aCL antibody binding correlated with poor performance on the water maze [52], suggesting a specific role for these autoantibodies.

Other mechanism by which APS antibodies may contribute to NPSLE manifestations are via endothelial activation and the induction of a prothrombotic state [53] or via directly affecting BBB permeability and thus allowing for the penetration of pathogenic autoantibodies such as anti-NR2 antibodies [54]. Further studies are needed to determine the primary mechanism of aCL antibodies and their effect on brain health.

3.4 Cytokines

Cytokines have been implicated in neurotoxicity. For example, when CSF from MRL/lpr mice was administered into the CNS of a nonautoimmune rat, it induced neurotoxicity and periventricular neurodegeneration [55]. Exposure to lupus CSF also led to reduced neuronal viability of hippocampal neurons and astrocytes *in vitro*, suggesting the presence of intrathecal neurotoxic metabolites and/or cytokines [56].

As described above, cytokines may directly act to breach the BBB [19]. For example, peripheral administration of lipopolysaccharide (LPS), a cytokine inducer, or of recombinant IL-1 and TNF-α is sufficient to decrease motor and social activity and reduce food and water intake, reflecting depression and anhedonia, respectively, in C57BL/6 mice [57, 58]. The effect was most likely mediated by TNFα, since mice deficient in TNF-α receptors was resistant to both depression and sickness behavior [59], although specific analyses separating peripheral from brain-specific effects were not done. Further supporting a role for cytokines is the

observation that increased serum levels of IL-1 correlated with blunted responsiveness to palatable stimulation in MRL/lpr mice [60]. Additionally, IL-6 production occurs early on and reduces sucrose preference, which is a behavioral alteration replicated by exogenous IL-6 administration [61]. IL-6 knockout mice are somewhat protected from the behavioral effects of LPS and IL-1 injection [62, 63], suggesting that IL-6, as TNFα, is acting downstream of these mediators. Furthermore, treatment with cyclophosphamide abolished the rise in IL-6, as well as attenuated behavioral deficits and neuronal death in MRL/lpr mice [64, 65]. Finally, injection of IL-6 increased BBB permeability in rats [66].

An additional possible player is TNF-like weak inducer of apoptosis, TWEAK. TWEAK is a secreted ligand of the TNF family that mediates its effects through its receptor Fn14, and Fn14-deficient MRL/lpr mice displayed decreased depressive behavior and cognitive impairment as measured by decreased immobility in forced swim test and maintained preference for sweetened fluids compared to controls [67]. Fn14 knockout mice also showed improved BBB integrity as measured by albumin quotient [67], suggesting a specific effect of TWEAK on the BBB.

Separate from the typical proinflammatory cytokines (TNFα, IL-1, and IL-6), IFNα may play an important role in NPSLE. IFNα is an antiviral cytokine in the type I IFN family strongly implicated in the pathogenesis of SLE. Numerous studies have shown that type I IFN receptor (IFNAR) deficiency reduces disease in multiple lupus mouse models [68–70]. Similarly, clinical data from patients undergoing IFNα therapy have shown neurotoxicity and induction of symptoms similar to those in NPSLE, such as cognitive impairment, seizures, and mood changes [71, 72]. In a bioassay containing plasmacytoid dendritic cells (the main INFα-producing cell type) and a source of antigen, CSF from NPSLE patients induced higher IFNα production than CSF from other autoimmune disease control subject [73], suggesting that specific antibodies and/or cytokines in CSF from SLE patients can stimulate IFNα production, although the nature of such stimulants remains unknown. Most recently, it was shown that treatment of NZB/W mice with anti-IFNAR antibodies effectively blocked neurological symptoms and that IFNα directly affected microglia cells *in vitro* [74]. Future studies evaluating the specific lack of IFNAR expression within the brain will be important to determine if the effect of IFNα in NPSLE is predominantly peripheral or brain specific. Furthermore, studies addressing the importance of IFNAR expression on specific brain-associated cell subsets *in vivo* during disease development are required to develop suitable BBB-breaching therapies if needed.

In addition to a direct effect of cytokines on the BBB, it is possible that cytokines can target the CNS without BBB disruption. This possibility stems from studies showing that cytokines do not need to pass the BBB to regulate behavior [75]. The existence of an entity called "sickness behavior," as characterized by lethargy, depression, malaise, and loss of appetite, supports the notion that immunity can affect behavior [57]. Sickness behavior is considered an adaptive response to infection that is mediated by cytokines, mainly IL-1, IL-6, and TNFα [75]. These cytokines have been separately implicated in the pathogenesis of psychiatric disease and are the same cytokines found to be elevated in MRL/lpr [76–78], NZB/W F1 [66, 79], and human [80] studies of NPSLE as described above.

There are two ways by which cytokines can affect the brain *without* involving BBB disruption. First, cytokines may enter the brain through afferent branches of the vagus nerve, which contain macrophages and dendritic cells in their sheath [81], and secondly, phagocytic cells in brain regions surrounding the ventricles and the choroid plexus may themselves produce and release cytokines [82]. Evidence for the role of the vagus nerve includes studies that show that vagotomy reduces sickness behavior [83, 84] and brain IL-1 expression [85–87] in response to intraperitoneal LPS and IL-1. This finding may be mediated through cytokine

production by immune cells in the vagus perineural sheath [81]. It has also been found that macrophage-like cells and microglia in the brain regions surrounding the ventricles and the choroid plexus, which lack BBB, produce IL-1 in response to LPS administration [88, 89]. Thus, although the prevailing hypothesis is that BBB dysfunction is necessary for NPSLE manifestation, data from sickness behavior and depression research suggest that there may be BBB-independent cytokine-mediated mechanisms.

In summary, cytokines contribute to NPSLE via a variety of mechanisms, including through the vagus nerve and periventricular brain regions without crossing the BBB, by directly causing BBB disruption, and/or by causing specific neurotoxicity.

3.5 Microglial activation

As the major immune cell type of the brain, microglia phagocytize redundant and unnecessary synaptic connections, thereby contributing to the structural organization of the brain and facilitating learning and memory [90]. Estrogen has been implicated in the pathogenesis of NPSLE via microglial activation. In female MRL/lpr mice, global estrogen receptor (ER) α deficiency resulted in reduced numbers of activated hippocampal microglia and improved spatial memory, as measured by the Morris water maze performance, in a manner independent of serum autoantibody and estrogen levels [91]. However, it remains unknown if this effect was direct or mediated by reduced immune reactivity.

Recently, it was shown that also IFNα stimulates microglial reactivity, and treatment of lupus-prone mice with anti-IFNAR antibody was sufficient to reduce percentages of activated microglia and synapse loss, as well as prevent behavioral phenotypes [74]. Moreover, increased IFNα signaling was also observed in postmortem hippocampal brain sections from patients [74], further supporting a pathogenic role for IFNα in NPSLE. Taken together, these data suggest that the pathogenesis of NPSLE may involve IFNα-driven and ER-mediated microglial activation.

4. Clinical phenotypes

4.1 Epidemiology

A prevalence as low as 12% and as high as 95% has been described for NPSLE manifestations. Different study designs, NPSLE symptoms studied, and population selection have contributed to discrepancies in reports.

The first set of standardized nomenclature was developed in 1999 by the American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. Case definitions were established for 19 different neuropsychiatric syndromes and divided into 12 central nervous system (CNS) and 7 peripheral nervous system (PNS) manifestations, as listed in **Table 1** [92]. The PNS manifestations are less common than CNS syndromes and are addressed elsewhere [93, 94]. CNS syndromes were further categorized into focal neurologic syndromes (cerebrovascular disease, seizures, myelopathy, aseptic meningitis, movement disorder, and demyelinating syndrome) and diffuse psychiatric/neuropsychological syndromes (cognitive dysfunction, mood and anxiety disorders, psychosis, acute confusional state, and headache).

As expected, the diffuse psychiatric/neuropsychological syndromes presented with more difficulties in diagnostic agreement due to their diverse presentations

	ACR criteria [92]	**Modified criteria by Ainiala [95]**
Central nervous system—manifestations	*Focal neurologic syndromes* Aseptic meningitis Cerebrovascular disease Demyelinating syndrome Movement disorder (chorea) Myelopathy Seizure disorders *Diffuse psychiatric/neuropsychologica syndromes* Headache (including migraine and benign intracranial hypertension) Acute confusional state Anxiety disorder Cognitive dysfunction Mood disorder Psychosis	Aseptic meningitis Cerebrovascular disease Demyelinating syndrome Movement disorder (chorea) Myelopathy Seizure disorders Acute confusional state Cognitive dysfunction (moderate or severe) Severe depression Psychosis
Peripheral nervous system—manifestations	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre´ syndrome) Autonomic disorder Mononeuropathy, single/multiplex Myasthenia gravis Neuropathy, cranial Plexopathy Polyneuropathy	Acute inflammatory demyelinating polyradiculoneuropathy Autonomic disorder Mononeuropathy, single/multiplex Myasthenia gravis Neuropathy, cranial Plexopathy Polyneuropathy (with ENMG confirmation)

Table 1.
ACR criteria for NPSLE syndromes.

and subjective nature [92]. In a subsequent cross-sectional validation study, these criteria were found to have a 46% specificity, thereby demonstrating inability of criteria to distinguish NPSLE patients from controls [95]. This low specificity was speculated to be partly attributed to the manifestations of NPSLE that overlap with other CNS conditions, as well as discrepancies in diagnosis of the diffuse neuropsychological syndromes. When the validation study excluded syndromes without any indication of neurologic dysfunction, including headache, mild cognitive dysfunction, mild mood and anxiety disorders, and polyneuropathy without electrophysiological confirmation, they were able to improve specificity to 91% [95].

To better understand the reasons for the high variability of prevalence estimates between different studies, Unterman et al. [96] performed a meta-analysis of 17 studies from 1999 to 2008 that applied the 1999 ACR case definitions. Using a subanalysis of 10 prospective studies, they found the prevalence of NP syndromes in SLE patients to be 56.3%, with a range from 23 to 95% [96]. In contrast, analyses of retrospective studies presented with a cumulative prevalence of only 17.6% [96]. A reason for this discrepancy may be that the syndromes that are more subjective to diagnose, such as headache, mood disorders, cognitive dysfunction, and anxiety, often had increased prevalence in prospective studies as compared to numbers obtained from retrospective studies [96]. In contrast, syndromes that may be considered more objective due to their measurability, such as seizures and movement disorders, showed little variability in prevalence from prospective versus retrospective studies and thus would be equally suitable for retrospective or prospective review.

Examination of studies at either end of the prevalence spectrum revealed several key characteristics influencing variability, including exclusion of subjective syndromes such as headache, differences in population characteristics such as age

and race, and the level of detail in diagnosis, including the use of a comprehensive neurocognitive battery [96]. It should be noted that of the 19 syndromes defined by the ACR, none is specific to NPSLE, and thus when assessing prevalence and impact, comparison to control populations and attribution to SLE versus other diseases are important.

NPSLE diagnosis is still currently a process of exclusion, which requires a detailed history and comprehensive evaluation to rule out other causes of symptoms, such as primary neurological or psychiatric disease [97]. Laboratory studies are important to support a NPSLE diagnosis, in particular markers of inflammation such as erythrocyte sedimentation rate and complement levels [97]. Of the serum autoantibodies, perhaps the most consistently present are the serum aPL, with an estimated prevalence of 45% in NPSLE patients [98, 99], although it should be noted that presence of these autoantibodies does not preclude the possibility of concurrent SLE and primary neuropsychological disease.

4.2 Cerebrovascular disease

Cerebrovascular disease stemming from SLE is thought to be at least partially caused by antiphospholipid (aPL) antibodies, leading to thrombosis in cerebral vasculature [1]. Identified risk factors for cerebrovascular disease include chronic and high disease activity, high cumulative corticosteroid dose, persistently elevated titers of aPL antibodies, heart valve disease, and systemic hypertension [100, 101]. An additional contributor to cerebrovascular disease is the observation of premature atherosclerosis in the vasculature of SLE patients, which occurs independently of traditional cardiovascular risk factors [102]. Data in support of this include increased prevalence of carotid plaque in SLE patients compared with age- and sex-matched controls even after adjustment for traditional risk factors [103]. A recent study shows that the relative risk of subclinical atherosclerosis in SLE was comparable to that found in diabetes mellitus, a well-known and major risk factor for cerebrovascular disease [104]. Cerebrovascular disease can lead to events such as stroke, which can then lead to other NPSLE syndromes such as cognitive dysfunction [105].

4.3 Seizures

Seizures often occur early in NPSLE disease progression and are positively correlated with African race/ethnicity, lower educational status, and cumulative organ damage [106]. The correlation with race and education may be a reflection of socioeconomic status [107], which is a predictor of both functional status and mortality [108] and may influence access and adherence to treatment [106]. In prospective cohort studies, the most common seizure type was primary generalized; however, some patients also had partial episodes [109, 110]. Cerebral atrophy and cerebrospinal fluid (CSF) pleocytosis are common findings in NPSLE, perhaps suggesting that there may be a lupus-related encephalopathic process seizure pathogenesis [93]. Independently of other symptoms, seizure occurrence can be an indicator of the level of disease activity [109, 111].

Seizures may occur many years before SLE diagnosis, potentially leading to erroneous diagnoses of epilepsy [109]. This misdiagnosis may be prevented by obtaining antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) levels, as these are commonly elevated in patients with seizures attributable to SLE [112] and would further support SLE as the etiology. In one larger prospective study, most seizures resolved without a negative impact on quality of life and did not require long-term antiseizure medication, although a smaller study

found a need for long-term continuous treatment with antiepileptics [113]. This discrepancy may be due to the latter study being retrospective, allowing for longer follow-up time. Seizure prevalence varies, as is the case with estimates of all NPSLE symptoms; however, most larger studies found a cumulative frequency of 5–10% of SLE patients [106, 109, 113].

It remains unclear if aPL antibodies are associated with seizure occurrence, as one study showed a positive correlation with seizure recurrence [114], while others did not [106, 111, 113]. Because antibody titers were not always measured close to seizure event time points, further studies are needed to better understand how antibodies may change with disease activity and therefore influence seizure occurrence. There is evidence, however, that antibodies may directly induce seizures by increasing neuronal excitability through inhibition of GABA receptors [115] and permeabilization and depolarization of brain synaptoneurosomes [116]; however, it is also possible that aPL antibodies lead to strokes, which predispose patients to seizures [111, 117]. Thus, aPL antibodies and strokes are confounding factors for seizure etiology [114].

Finally, consistent evidence supports a protective effect of antimalarials for seizure occurrence as well as overall survival [106, 118]. Evidence for a mechanism includes studies that show antimalarials interfering with interferon-α production and immune complex formation by preventing incorporation of RNA and DNA fragments into Toll-like receptors 7 and 9, respectively [119, 120]. Authors have also found lipid-lowering effects of antimalarials via interference with lipoprotein lipase activity [121–123]. Lastly, antithrombotic properties of antimalarials have been demonstrated in both mice [124] and patients [125, 126]. Thus, protection from seizures with the use of antimalarial agents may be related to the prevention of thrombosis.

4.4 Myelopathy and demyelination syndrome

Myelopathy is a general term used to describe any disorder of the spinal cord leading to paraparesis and/or sensory impairment, which can arise from a number of etiologies, such as ischemia, compression, metabolic, and inflammatory causes [127]. Myelitis technically refers to when a spinal lesion is secondary to inflammation; however, the two are often used interchangeably in the literature [127]. In the 1999 ACR criteria (see **Table 1**), myelopathy and demyelination syndrome are considered separate entities, with myelopathy referring to any rapidly involving spinal cord lesion, whereas demyelination syndrome encompassed demyelinating lesions anywhere in the CNS, which includes transverse myelopathy [92]. Due to the considerable overlap in these two syndromes, they will be considered together here.

Myelopathy in NPSLE usually refers to transverse myelitis (TM), which is an early, rapidly evolving but very rare manifestation (~1%) [96, 97]. The mechanism can be ischemic or inflammatory in nature, and symptoms typically manifest as flaccidity and hyporeflexia or spasticity and hyperreflexia [128]. Transverse myelopathy has been identified as the first manifestation of SLE [129] and has been associated with aPL positivity [130], suggesting aPL-induced thrombosis as a potential mechanism [131]. The evidence, however, has not been consistent [132, 133], and the presence of thrombosis does not explain involvement of different levels of the spinal cord [134]. Some have suggested an aPL-induced vasculitis of spinal vessels [135] and loss of perfusion secondary to spinal cord swelling [128] as alternative mechanisms.

Demyelinating syndrome in lupus has been termed lupus sclerosis to indicate the clinical similarities with MS, such as optic neuritis, brainstem and cerebellar syndromes, spastic paraplegia, and other transient neurological deficits [93].

The term "clinically isolated syndrome" was originally developed to describe the first demyelinating episode suggestive of MS [136], but it could also be the first demyelinating episode of NPSLE [134]. Pathological studies confirmed that lupus sclerosis was indeed distinct from MS, with no evidence of primary demyelination [137]. Misdiagnosis can have disastrous consequences, as treatments for MS, especially interferon-based therapies, can exacerbate SLE [138]. Certain clinical findings, such as the concomitant presence of renal involvement, rash, arthritis, myalgia, PNS involvement, and meningismus, might indicate SLE as the underlying diagnosis [134]. Moreover, the presence of cerebrovascular disease or thrombotic events is the clue for concomitant or primary APS [139]. In fact, one study found that 8% of patients with aPL positivity had a previous diagnosis of MS or MS-like symptoms [140], suggesting that aPL screening should be conducted in patients presenting with MS-like symptoms, particularly since it is noninvasive and inexpensive [134, 141].

Additionally, high ESR, ANA, and lack of oligoclonal immunoglobulin bands in the CSF would support NPSLE etiology. Whereas type I IFN activity is elevated in SLE and implicated in its pathogenesis, type I IFN activity is low in MS [142] and IFNβ is actually used as a treatment for MS [143]. This difference suggests that measuring serum type I IFN activity may be a useful way to distinguish patients who have demyelinating syndrome from SLE versus MS [142].

Optic neuritis in NPSLE is characterized by pain with ocular movements and visual impairment [134], and similarly, TM can be the first presentation of SLE and has been associated with aPL [144]. The combination of TM and optic neuritis is termed neuromyelitis optica (NMO). In a small cohort of SLE patients with white matter myelitis, NMO was found in roughly half of the patient population [128]. Interestingly, NMO is also associated with aPL positivity in addition to the presence of antiaquaporin autoantibodies [128, 145]. Antiaquaporin antibodies are specific to NMO and present in the sera of SLE patients years before the first NMO attack [146]. Additionally, serum IFNα activity was found to be high in NMO patients, similarly to patients with SLE [142], suggesting that NMO and SLE may share at least some similarities in pathophysiology.

NMO was only recently recognized to be an independent entity rather than a subset of MS [145, 147]. Additionally, because TM, optic neuritis, and NMO all have associations with aPL positivity, studies have suggested an intersection between SLE, MS, and APS [138, 141, 148]. Given that the literature on myelopathy in SLE still consists of mostly case studies [129, 130, 149–152], larger cohort studies are needed to better characterize these patients and distinguish pathogenesis of myelopathy from SLE versus MS. Additionally, a considerable amount of knowledge has been gained in the past two decades about various forms of myelopathy, and it is reasonable to consider reorganizing these syndromes in a revision of the 1999 ACR classification system [153].

4.5 Aseptic meningitis

Aseptic meningitis is a rare feature of NPSLE, but when it does present, it is usually earlier in the disease course and may signal the advent of other CNS complications such as transverse myelitis and strokes [93]. Diagnosis usually involves leukocytosis evident on cerebrospinal fluid analysis. Notably, nonsteroidal antiinflammatory drugs (NSAIDs) can cause aseptic meningitis [93]. Anywhere from 25 to 84% of lupus patients are treated with NSAIDs for symptoms such as synovitis, serositis, fever, soft tissue pain, and headache [154], making it difficult to determine the initiating factor. Regardless, many patients who experience drug-induced aseptic meningitis have SLE, suggesting that there may be some inherent

predisposition, although the mechanism is unknown [155]. In summary, adverse medication events may complicate the diagnosis of primary versus treatment-induced aseptic meningitis. Drug discontinuation is currently the only method to distinguish between these, as complete recovery can be observed after several days of drug discontinuation in drug-induced aseptic meningitis [155].

4.6 Movement disorders

Movement disorders in SLE are infrequent in adult NPSLE patients (<2%), although more frequently observed in juvenile SLE. When it occurs, it is often associated with an acute flare and predominantly in women under the age of 30 years [93]. Manifestations include rigidity, tremors, masked facies, chorea, and akinesia, although symptoms are often transient in nature [93, 97].

4.7 Cognitive dysfunction

In 1999, the ACR committee proposed a standard 1-hour battery of neuropsychological tests to assess cognitive function [92], which has since been tested and established for reliability and validity [156]. The definition of dysfunction included significant deficits in simple or complex attention, reasoning, executive skills, memory, visual-spatial processing, language, or psychomotor speed [92]. Studies have used different types and lengths of neuropsychological testing, thus contributing to a wide range of prevalence anywhere from 0 to 80% [156]. When the 1-hour battery as proposed by the ACR is used, the prevalence of cognitive dysfunction has a narrower range of between 23 and 60% [156].

Cardiovascular risk factors have been found to be related to the severity of cognitive dysfunction in SLE, in particular hypertension, which is also a risk factor for cognitive impairment in the general population [105]. In addition, hypertension itself has been associated with brain atrophy and cognitive dysfunction [157] and thus may contribute to the risk of cognitive dysfunction independently of SLE. Because cognitive impairment is also a common sequela of stroke [158], the association with aPL positivity may in fact be due to an occlusive vasculopathy [49]. Thus, screening for cardiovascular risk factors in SLE patients presenting with aPL positivity is important, as the risk for stroke may be significantly increased above baseline in these patients. Furthermore, this finding emphasizes that cognitive dysfunction is often sequelae of cerebrovascular events and may be prevented in some cases by addressing hypercoagulability and cardiovascular risk in SLE patients.

4.8 Mood changes

Mood changes in NPSLE encompass major depressive-like episodes, mood disorders with depressive, manic or mixed features, anxiety, panic disorders, and compulsion, with depression being the most common [97]. Not surprisingly, SLE disease activity is correlated with the presence and severity of major depression [159]. This connection may be a result of a multitude of mechanisms, including an independent association between mood and cardiovascular risk factors [100], as well as the psychological burden of having SLE in the first place, including illness stigma [160]. As discussed previously, elevated cytokine levels may also contribute to depression and anhedonia in NPSLE patients [75].

Similarly to psychosis (see below), it is important to determine if mood disorders are a result of primary psychiatric disease or secondary to corticosteroid therapy, as studies have shown a correlation between corticosteroid usage and several mood disorders [161–164]. Mania seems to be more commonly caused by

acute corticosteroid therapy [161, 163], whereas long-term therapy is more likely to lead to depressive symptoms [164]. Psychiatric disorders typically occur within the first 6 weeks of corticosteroid treatment and are dose dependent [161]. Up to 90% of patients recover completely with discontinuation or a reduction in dosage [161]. Additionally, when mood disorders are the initial presentation of NPSLE, corticosteroids are not typically used. Rather, patients usually receive antidepressant and antipsychotic medications, which are effective in treating mood disorders secondary to NPSLE [162]. Thus, corticosteroid-induced mood changes are a confounding factor only when mood changes develop after NPSLE diagnosis and subsequent steroid therapy, and withdrawal of steroids and use of antidepressant/antipsychotic medications would be warranted at that time. Factors that would suggest an SLE etiology rather than an iatrogenic one include the presence of a chronological association, imaging and EEG abnormalities, non-CNS manifestations of SLE, and serious disturbances in memory and concentration [162].

4.9 Lupus psychosis

Psychosis is a disturbance in perception of reality usually characterized by delusions and/or hallucinations, in the absence of delirium, and causing significant distress or functional impairment [165]. Psychosis is a relatively rare event in SLE that, similarly to seizures, occurs early and transiently in disease course, if at all [144, 166]. The reported prevalence varies from 0 to 11% [167–169].

The ACR Committee adopted terminology from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [170], and lupus psychosis falls under "psychosis due to a general medical condition" (DSM-IV 293.81/82), which excludes schizophrenia and brief psychotic disorder, as well as bipolar disorder [170]. Thus, NPSLE patients with psychosis secondary to schizophrenia, brief psychotic disorder, or bipolar disorder, although few, would not be captured under the category of lupus psychosis per strict ACR case definitions [166].

In a retrospective study of 11 patients with primary lupus psychosis and a mean follow-up of 13 years, all had good response to intensive immunosuppressive treatment at the time of diagnosis and 70% achieved complete remission, suggesting a favorable long-term prognosis [166]. When diagnosing patients, it is important to distinguish lupus psychosis from iatrogenic steroid psychosis, for which hypoalbuminemia may be a risk factor [171]. Steroid psychosis is typically dose-dependent, occurs within 8 weeks of initiation, and usually resolves completely with dose reduction [162]. It should be noted that SLE itself is linked to a higher risk of steroid psychosis, possibly related to BBB damage, another risk factor for steroid psychosis. Therefore, it is important to identify new clinical readouts that are more suggestive of NPSLE, such as non-CNS manifestations, severe deficits in memory and concentration, or focal neurologic deficits [162]. Moreover, there are a number of agents that can be used for prophylaxis of steroid-induced neuropsychiatric disorders; thus, if steroid therapy is unavoidable, concurrent administration with valproate and lithium should be considered.

4.10 Acute confusional state

Acute confusional state is synonymous with encephalopathy and is characterized by impaired consciousness or level of arousal, which can progress to coma [172]. It is rarer than the other CNS syndromes, with a reported prevalence of 4–7% of SLE patients [173]. The etiology of acute confusional state in SLE remains to be determined, as SLE-nonspecific events such as infections and metabolic disturbances can also cause this syndrome [174].

4.11 Headache

In a meta-analysis of 35 studies of headache in NPSLE, the prevalence of all headache types, including migraine, was not different from controls, and insufficient evidence was found for the concept of "lupus headache" [175, 176]. Additionally, no specific mechanism for headache in SLE patients exists, and there is no link between headache and disease activity or cumulative organ damage [175, 177]. Pooled prevalence in this meta-analysis was 50.2%, in contrast to a much lower 12.2% in a more recent meta-analysis [96]. The estimate is closer to 30% if only prospective and elicited studies are included [96], suggesting that there is either underreporting in retrospective reviews or perhaps a component of recall bias in prospective studies. Additionally, it has been observed that headache prevalence can vary considerably with cultural differences, as Asian populations tend to report headache less frequently [178].

A recent prospective study of an international cohort found no link between headache and specific autoantibodies at time of study enrollment [177]. Although headaches negatively impacted quality of life, most headaches resolved independently of lupus-specific therapies [177], further supporting the lack of evidence for "lupus headache." There is inconsistency in diagnosing headache associated with SLE, even by physicians who specialize in SLE, and it remains unclear whether headache in SLE patients exists as an entity independent of other NPSLE events, such as meningitis, seizure, and cerebrovascular disease, and whether it warrants measurement as included in ACR criteria [175, 177].

The International Headache Society (IHS) has established criteria for the classification of all headaches, and in a 2008 study, they were found to be more exhaustive than current ACR criteria and include categories such as chronic headache disorders, which were not included in the ACR criteria [176]. Thus, some headache disorders may not be classified [176]. Discrepancies in headache classification may also explain prevalence variance. Additionally, cluster headaches are included in the criteria but evidence for its existence in NPSLE is sparse. This weakness suggests that ACR criteria may be in need of revision, especially given that IHS criteria is already used as the basis for clinical trials of headache treatments.

4.12 Summary

In conclusion, the clinical syndromes of NPSLE are varied and each presents with challenges in diagnosis and classification. The ACR criteria are in need of an update to offer more specificity, as pathogenetic mechanisms cannot be elucidated if there is no consensus about which patients have the syndrome. Because none of the syndromes discussed above are unique to NPSLE, there are often already preexisting classification criteria, such as those for headaches and psychosis. As such, it is important in future studies to adhere to more stringent and consistent criteria rather than using inconsistent classification or evaluation methods. This approach would likely also limit the high variability in prevalence estimates of all NPSLE syndromes, notwithstanding the already subjective nature of many of these syndromes as well as differences in population characteristics. Many of these syndromes, such as seizures, myelopathy, and psychosis, present early on and can be the initial manifestation of NPSLE. Thus, as is the case with any disease, successful diagnosis of NPSLE starts with its inclusion on the list of differentials, although it remains a diagnosis of exclusion due to the lack of consistent biomarkers. A recent review detailed a diagnostic algorithm incorporating ACR case definitions and results from other studies suggesting modifications [94], and use of this may likely improve diagnostic accuracy and precision of prevalence estimates for future studies.

5. Evaluation and diagnosis

5.1 Imaging

A variety of imaging modalities are available for use in patient evaluation, including both anatomical imaging, such as CT, MRI, and magnetization transfer imaging, as well as functional imaging, such as functional MRI, PET, and SPECT imaging [97]. For a review of the most prevalent findings in NPSLE for each modality, see the review by Jeltsch-David and Muller [97]. As expected, the focal neurologic syndromes, namely seizures, cerebrovascular disease, myelopathy, and demyelinating syndrome, have the most identifiable imaging manifestations. MRI is perhaps the most commonly used technique due to its availability and popularity as an anatomical imaging modality, despite its poor sensitivity and specificity for NPSLE [97]. Additionally, MRI is often used in the workup of primary neurological diseases and is necessary to exclude these in the etiology of symptoms. For example, MRI can help to exclude infection and malignancy [131], and since NPSLE is a diagnosis of exclusion, MRI is a necessary part of the evaluation. Additionally, specific MR sequences with fluid attenuated inversion recovery and diffusion weighted imaging are recommended to improve sensitivity and specificity [93].

5.2 Biomarkers

Patient evaluation consists of first collecting a detailed medical history and ensuring exclusion of more common etiologies of NPSLE symptoms prior to chasing a diagnosis of neurolupus [97]. Only then, it is worthwhile to pursue broad laboratory investigation, such as CSF analysis, complement levels, erythrocyte sedimentation rate, as well as autoantibody panels. Identification of reliable biomarkers remains elusive, hence the continued need for pathogenetic inquiry [97]. Mechanisms are complex, and due to the diversity of presentations, no single pathway has been identified as a sole marker of disease. However, some commonalities include BBB dysfunction, vascular occlusion, neuroendocrine-immune imbalance, tissue damage mediated by autoantibodies and proinflammatory cytokines, and direct neuronal cell death [97]. Additionally, it is important to consider the heterogeneity of the studied population and assays used to assess antibody levels [179].

Antibodies to consider measuring include those targeting phospholipids, ribosomal P peptides, glial fibrillary acidic protein (GFAP), NMDA receptor, microtubule-associated protein 2 (MAP-2), and matrix metalloproteinase 9 (MMP-9). As outlined above, many of these have also been identified in animal models of NPSLE, further supporting potential causative and/or diagnostic relationships. Details on the specificity and association of each of these antibody specificities with each NPSLE syndrome were recently summarized [97]. In a recent meta-analysis of 41 studies of serum and CSF autoantibodies in NPSLE, significantly more NPSLE patients demonstrated positivity for serum aCL Abs, LA Abs, anti-RP Abs, antineuronal Abs, and CSF antineuronal antibodies as compared to SLE patients [50]. Thus, they suggest that measurement of these antibodies may help to identify patients at the risk of developing NPSLE.

It is important to note that multiple measurements of antibodies are needed for the most complete assessment, as antibody levels have been shown to fluctuate with time and disease activity (flares) [179]. Specific testing recommended for each syndrome is detailed elsewhere [131]. Measurement of aPL antibodies is warranted particularly if patients present with cerebrovascular disease, seizures, myelopathy, or cognitive dysfunction, as aPL-induced thrombosis is implicated in the

pathogenesis of these conditions. Positivity for aPL also influences management, as discussed further below.

Importantly, none of these antibodies have an adequately consistent association to qualify as a reliable biomarker, with even the most studied antibodies peaking at around 50% for prevalence in patients with NPSLE [97]. For example, antiribosomal P antibodies generated a great deal of interest, due to its early discovery in patients with lupus psychosis [41]. However, although early studies found diagnostic value, more recent studies shed doubt on its accuracy for NPSLE diagnosis [20]. A handful of cytokines, however, do show promise as being consistently elevated, among which is the aforementioned IFNα [73, 97]. Thus, more research is needed to determine if IFNα or other cytokines, such as IL-6, IL-8, and IL-10, would be suitable biomarkers or markers of disease activity.

6. Management

Due to the dearth of controlled trials for NPSLE therapy, current clinical practice is still defined by either addressing inflammation with immunosuppressive medication or ischemia and thrombotic events with anticoagulants [180]. Immunosuppression, which is still currently the mainstay of treatment for NPSLE, consists of corticosteroids alone or in combination with a second immunosuppressive agent [131]. Options for additional immunosuppression include cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, rituximab, intravenous immunoglobulins, therapeutic plasma exchange, and hematopoietic stem cell transplant as a last resort [131]. Because corticosteroids have the most immediate antiinflammatory effect, they are often used in treatment of SLE disease flares, although dosing is still often empirical [181]. In addition to the previously discussed side effects of mood disturbances and psychosis, glucocorticoids can also cause hypertension, dyslipidemia, and increase the already elevated risk for cerebrovascular events in SLE [182]. Keeping doses <7.5 mg/day as well as the use of methylprednisolone pulses rather than long-term steroid therapy may help to mitigate the long-term adverse effects [183]. Thus, steroid therapy for NPSLE should be administered judiciously, and it may be prudent to use the minimum effective dose and titrate up as needed, reserving the higher doses for the acute setting.

Of the other immunosuppressive agents, cyclophosphamide was the only one tested in a randomized controlled clinical trial in acute, severe NPSLE, which found that treatment response was higher in the cyclophosphamide group versus the methylprednisolone group [184]. However, a subsequent Cochrane review categorized this study as low quality evidence due to its small size and high risk of allocation concealment, blinding, and selective reporting [185], thus highlighting the need for more high-quality randomized controlled trials evaluating the different immunosuppressive agents. Of the remaining options, azathioprine is most often used clinically as maintenance therapy following cyclophosphamide induction due to its milder side effect profile, and rituximab is used as a second-line therapy for severe, refractory NPSLE, although none of these agents have sufficient high-quality evidence to support their use [131].

Symptomatic therapy, which does not address the underlying pathology of NPSLE, is often the first treatment for SLE patients presenting with NP symptoms due to a lack of recognition of NPSLE [131]. Examples include antidepressive and antipsychotic agents for mood disturbances and psychosis, antiepileptics for seizures, dopamine agonists for movement disorders, and NSAIDs for headache [131]. These agents can be sufficient for symptomatic control in those with mild NPSLE disease. In those experiencing cognitive dysfunction or mood disturbances

secondary to the psychological burden of disease, psychoeducational group interventions may be beneficial [186, 187].

Primary prevention strategies, defined as preventing the onset on NPSLE, have been suggested with the use of hydroxychloroquine [144, 188], which is advantageous since hydroxychloroquine is a widely used and safe therapy for SLE [131]. As discussed previously, antimalarials are associated with less damage accrual [189] and have been shown to reduce mortality [118, 190], reduce cardiovascular disease and thrombotic risk [122, 123], and protect against seizures [106]. Statins may affect the regulation of inflammatory processes leading to atherosclerosis [191] and thus would be a reasonable agent to consider in the primary prevention of cerebrovascular events in NPSLE. However, a 2-year trial of statin therapy showed no benefit in primary or secondary atherosclerosis outcomes in SLE patients [192]. Accordingly, statins should be started in NPSLE patients with hyperlipidemia who meet criteria based on current cardiovascular disease guidelines [131]. Lastly, antiplatelet agents and anticoagulants are crucial for primary and secondary prevention of thrombotic complications in NPSLE patients [131]. Recommendations from a task force published in 2011 state that SLE patients with medium-high titers of aPL-antibodies should receive primary thromboprophylaxis with hydroxychloroquine and low-dose aspirin [193]. In a more recent randomized controlled trial of 166 SLE patients with aPL, no difference in thrombosis rate was found between those that received low-dose aspirin versus low-dose aspirin plus low-intensity warfarin [194]. Those with aPL-antibodies should also receive low-molecular-weight heparin for prophylaxis during high-risk situations, such as surgery or prolonged immobilization [193]. Low-dose aspirin is still recommended in patients with aPL even if they do not have SLE [193]. Patients diagnosed with APS following a thrombotic event should receive heparin followed by long-term anticoagulation with warfarin [193]. It is worth noting that the newer direct oral anticoagulants (DOACs), such as thrombin inhibitor dabigatran and antifactor Xa inhibitors rivaroxaban and apixaban, may be advantageous due to their fixed dosing and more predictable anticoagulant effects as compared to warfarin. Currently, insufficient evidence exists to recommend their use in APS, SLE and NPSLE, although ongoing trials are investigating their efficacy in APS specifically [195].

6.1 Potential future therapies

In addition to the lack of evidence for the use of broad immunosuppression in NPSLE, many of the drugs described above have an array of adverse and potentially debilitating side effects [131]. This emphasizes the need for more targeted therapies that may have greater efficacy in additional to minimizing the side effect profile. Some future candidates include factors implicated in BBB dysfunction, such as TWEAK, a pro-inflammatory cytokine in the TNF superfamily, as well as eculizumab, a humanized monoclonal antibody that blocks terminal complement generation, which again interferes with BBB integrity [131].

Of the potential future targets, perhaps the most promising is IFNα. Treatment with anti-IFNα antibodies has been shown to reduce SLE disease activity [196], and as previously discussed, IFNα has been consistently implicated in mouse models [68, 74, 197] and patients [73, 198] with NPSLE. More recently, anifrolumab, a type I IFN-receptor antagonist, was explored as a treatment option for moderate to severe SLE [199]. Unfortunately, patients with CNS syndromes were excluded in this study. Given the evidence for a pathogenic role of IFNα in mouse models of SLE and the identification of elevated IFNα levels in NPSLE patients, it will be important to study the response to anifrolumab therapy in NPSLE patients [74].

7. Conclusion

In summary, NPSLE is a debilitating disease that affects a number of SLE patients. Due to diverse presentations and overlap with other diseases, it is a particularly challenging entity to characterize and study. Here, we have reviewed the basic science, including commonly used mouse models, the involvement of the BBB, autoantibodies, cytokines, and microglial activation. We have also covered the various clinical phenotypes, emphasizing the wide range in reported prevalence, lack of suitable biomarkers, and steps in evaluation and management. The information presented herein calls for further research into the basic mechanisms driving NPSLE to ultimately improve quality of life for patients with this disease.

Acknowledgements

This work was funded in part by the Cleveland Clinic Foundation and a grant from the NIH (1R0AI118774) supporting work associated with studies of IFNα in lupus.

Conflict of interest

The authors declare no conflict of interest.

Author details

Emily Zhang[1,2] and Trine N. Jorgensen[1,2]*

1 Cleveland Clinic at Lerner College of Medicine at Case Western Reserve University, USA

2 Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, USA

*Address all correspondence to: jorgent@ccf.org

References

[1] Jeltsch-David H, Muller S. Neuropsychiatric systemic lupus erythematosus and cognitive dysfunction: The MRL-lpr mouse strain as a model. Autoimmunity Reviews. 2014;**13**(9):963-973. DOI: 10.1016/j.autrev.2014.08.015

[2] Pikman R, Kivity S, Levy Y, Arango M-T, Chapman J, Yonath H, et al. Neuropsychiatric SLE: From animal model to human. Lupus. 2017;**26**:470-477. DOI: 10.1177/0961203317694261

[3] Watson ML, Rao JK, Gilkeson GS, Ruiz P, Eicher EM, Pisetsky DS, et al. Genetic analysis of MRL-lpr mice: Relationship of the Fas apoptosis gene to disease manifestations and renal disease-modifying loci. The Journal of Experimental Medicine. 1992;**176**(December):1645-1656. DOI: 10.1084/jem.176.6.1645

[4] Gao H-X, Campbell SR, Cui M-H, Zong P, Hwang J-H, Gulinello M, et al. Depression is an early disease manifestation in lupus-prone MRL/lpr mice. Journal of Neuroimmunology. 2009;**207**(1-2):45-56. DOI: 10.1016/J.JNEUROIM.2008.11.009

[5] Malatynska E, Steinbusch HWM, Redkozubova O, Bolkunov A, Kubatiev A, Yeritsyan NB, et al. Anhedonic-like traits and lack of affective deficits in 18-month-old C57BL/6 mice: Implications for modeling elderly depression. Experimental Gerontology. 2012;**47**(8):552-564. DOI: 10.1016/J.EXGER.2012.04.010

[6] Sled JG, Spring S, van Eede M, Lerch JP, Ullal S, Sakic B. Time course and nature of brain atrophy in the MRL mouse model of central nervous system lupus. Arthritis and Rheumatism. 2009;**60**(6):1764-1774. DOI: 10.1002/art.24523

[7] Sakic B, Kolb B, Whishaw IQ, Gorny G, Szechtman H, Denburg JA. Immunosuppression prevents neuronal atrophy in lupus-prone mice: Evidence for brain damage induced by autoimmune disease? Journal of Neuroimmunology. 2000;**111**(1-2):93-101. DOI: 10.1016/S0165-5728(00)00364-7

[8] Ward MM. Prevalence of physician-diagnosed systemic lupus erythematosus in the United States: Results from the Third National Health and Nutrition Examination Survey. Journal of Women's Health Care. 2004;**13**(6):713-718

[9] Gao HX, Sanders E, Tieng AT, Putterman C. Sex and autoantibody titers determine the development of neuropsychiatric manifestations in lupus-prone mice. Journal of Neuroimmunology. 2010;**229**(1-2):112-122. DOI: 10.1016/j.jneuroim.2010.07.020

[10] Drake CG, Al DET. Genetic contributions to lupus-like disease in (NZB × NZW)F1 mice. Immunological Reviews. 1995;(144):51-74. DOI: 10.1111/j.1600-065X.1995.tb00065.x

[11] Roubinian JR. Effect of castration and sex hormone treatment on survival, anti-nucleic acid antibodies, and glomerulonephritis in NZB/NZW F1 mice. The Journal of Experimental Medicine. 1978;**147**(6):1568-1583. DOI: 10.1084/jem.147.6.1568

[12] Sthoeger ZM, Zinger H, Mozes E. Beneficial effects of the anti-oestrogen tamoxifen on systemic lupus erythematosus of (NZB × NZW)F1 female mice are associated with specific reduction of IgG3 autoantibodies. Annals of the Rheumatic Diseases. 2003;**62**(4):341-346. DOI: 10.1136/ARD.62.4.341

[13] Schrott LM, Crnic LS. Anxiety behavior, exploratory behavior, and

activity in NZB × NZW F1 hybrid mice: Role of genotype and autoimmune disease progression. Brain, Behavior, and Immunity. 1996;**10**:260-274

[14] Kier AB. Clinical neurology and brain histopathology in NZB/NZW F1 lupus mice. Journal of Comparative Pathology. 1990;**102**:165-177

[15] Alexander J, Jacob A, Quigg RJ. Effects of conventional immunosuppressive therapy on functional and pathological features of CNS lupus in NZB/W mice. F1000Research. 2015;**1656816568**:163163163-163163164. DOI: 10.12688/f1000research.6568.1

[16] Bracci-Laudiero L, Aloe L, Lundeberg T, Theodorsson E, Stenfors C. Altered levels of neuropeptides characterize the brain of lupus prone mice. Neuroscience Letters. 1999;**275**(1):57-60. DOI: 10.1016/S0304-3940(99)00737-5

[17] Hahn BH, Singh RR, Wong WK, Tsao BP, Bulpitt K, Ebling FM. Treatment with a consensus peptide based on amino acid sequences in autoantibodies prevents T cell activation by autoantigens and delays disease onset in murine lupus [Internet]. Arthritis & Rheumatism. 2001;**44**:432-441

[18] Diamond B, Volpe BT. A model for lupus brain disease. Immunological Reviews. 2012;**248**(1):56-67. DOI: 10.1111/j.1600-065X.2012.01137.x

[19] Stock AD, Gelb S, Pasternak O, Ben-Zvi A, Putterman C. The blood brain barrier and neuropsychiatric lupus: New perspectives in light of advances in understanding the neuroimmune interface. Autoimmunity Reviews. 2017;**16**:612-619. DOI: 10.1016/j.autrev.2017.04.008

[20] Karassa FB, Afeltra A, Ambrozic A, Chang D-M, De Keyser F, Doria A, et al. Accuracy of anti-ribosomal P protein antibody testing for the diagnosis of neuropsychiatric systemic lupus erythematosus: An international meta-analysis. Arthritis and Rheumatism. 2006;**54**(1):312-324. DOI: 10.1002/art.21539

[21] Rekvig OP, Putterman C, Casu C, Gao H-X, Ghirardello A, Mortensen ES, et al. Autoantibodies in lupus: Culprits or passive bystanders? Autoimmunity Reviews. 2012;**11**:596-603. DOI: 10.1016/j.autrev.2011.10.021

[22] McConnell HL, Kersch CN, Woltjer RL, Neuwelt EA. The translational significance of the neurovascular unit. The Journal of Biological Chemistry. 2017;**292**(3):762-770. DOI: 10.1074/jbc.R116.760215

[23] Iadecola C. The neurovascular unit coming of age: A journey through neurovascular coupling in health and disease. Neuron. 2017;**96**(1):17-42. DOI: 10.1016/J.NEURON.2017.07.030

[24] Muoio V, Persson PB, Sendeski MM. The neurovascular unit-concept review. Acta Physiol. 2014;**210**:790-798. DOI: 10.1111/apha.12250

[25] Johanson CE, Stopa EG, McMillan PN. The Blood-Cerebrospinal Fluid Barrier: Structure and Functional Significance. New York: Humana Press; 2011. pp. 101-131. DOI: 10.1007/978-1-60761-938-3_4

[26] Gulati G, Iffland PH, Janigro D, Zhang B, Luggen ME. Anti-NR2 antibodies, blood-brain barrier, and cognitive dysfunction. Clinical Rheumatology. 2016;**35**(12):2989-2997. DOI: 10.1007/s10067-016-3339-1

[27] Gelb S, Stock AD, Anzi S, Putterman C, Ben-Zvi A. Mechanisms of neuropsychiatric lupus: The relative roles of the blood-cerebrospinal fluid barrier versus blood-brain barrier. Journal of Autoimmunity. 2018;**91**:34-44. DOI: 10.1016/j.jaut.2018.03.001

[28] Sidor MM, Sakic B, Malinowski PM, Ballok DA, Oleschuk CJ, Macri J. Elevated immunoglobulin levels in the cerebrospinal fluid from lupus-prone mice. Journal of Neuroimmunology. 2005;**165**(1-2):104-113. DOI: 10.1016/J.JNEUROIM.2005.04.022

[29] Jacob A, Hack B, Chiang E, Garcia JGN, Quigg RJ, Alexander JJ. C5a alters blood-brain barrier integrity in experimental lupus. The FASEB Journal. 2010;**24**(6):1682-1688. DOI: 10.1096/fj.09-138834

[30] Ma X, Foster J, Sakic B. Distribution and prevalence of leukocyte phenotypes in brains of lupus-prone mice. Journal of Neuroimmunology. 2006;**179**(1-2):26-36. DOI: 10.1016/J.JNEUROIM.2006.06.023

[31] Alexander JJ, Bao L, Jacob A, Kraus DM, Holers VM, Quigg RJ. Administration of the soluble complement inhibitor, Crry-Ig, reduces inflammation and aquaporin 4 expression in lupus cerebritis. Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease. 2003;**1639**(3):169-176. DOI: 10.1016/J.BBADIS.2003.09.005

[32] Stanojcic M, Loheswaran G, Xu L, Hoffman SA, Sakic B. Intrathecal antibodies and brain damage in autoimmune MRL mice. Brain, Behavior, and Immunity. 2010;**24**(2):289-297. DOI: 10.1016/J.BBI.2009.10.009

[33] Perez-Otano I, Schulteis CT, Contractor A, Lipton SA, Trimmer JS, Sucher NJ, et al. Assembly with the NR1 subunit is required for surface expression of NR3A-containing NMDA receptors. The Journal of Neuroscience. 2001;**21**(4):1228-1237. DOI: 10.1523/JNEUROSCI.21-04-01228.2001

[34] Degiorgio LA, Konstantinov KN, Lee SC, Hardin JA, Volpe BT, Diamond B. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. Nature Medicine. 2001;7(11):1189-1193. DOI: 10.1038/nm1101-1189

[35] Williams S, Stafford P, Hoffman SA. Diagnosis and early detection of CNS-SLE in MRL/lpr mice using peptide microarrays. BMC Immunology. 2014;**15**(1):23. DOI: 10.1186/1471-2172-15-23

[36] Ozawa S, Kamiya H, Tsuzuki K. Glutamate receptors in the mammalian central nervous system. Progress in Neurobiology. 1998;**54**(5):581-618. DOI: 10.1016/S0301-0082(97)00085-3

[37] Lauvsnes MB, Omdal R. Systemic lupus erythematosus, the brain, and anti-NR2 antibodies. Journal of Neurology. 2012;**259**:622-629. DOI: 10.1007/s00415-011-6232-5

[38] Kowal C, Degiorgio LA, Lee JY, Edgar MA, Huerta PT, Volpe BT, et al. Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**(52):19854-19859. DOI: 10.1073/pnas.0608397104

[39] Hirohata S, Arinuma Y, Yanagida T, Yoshio T. Blood-brain barrier damages and intrathecal synthesis of anti-N-methyl-D-aspartate receptor NR2 antibodies in diffuse psychiatric/neuropsychological syndromes in systemic lupus erythematosus. Arthritis Research & Therapy. 2014;**16**(2):R77. DOI: 10.1186/ar4518

[40] Faust TW, Chang EH, Kowal C, Berlin R, Gazaryan IG, Bertini E, et al. Neurotoxic lupus autoantibodies alter brain function through two distinct mechanisms. Proceedings

of the National Academy of Sciences of the United States of America. 2010;**107**(43):18569-18574. DOI: 10.1073/pnas.1006980107

[41] Bonfa E, Golombek SJ, Kaufman LD, Skelly S, Weissbach H, Brot N, et al. Association between lupus psychosis and antiribosomal P protein antibodies. The New England Journal of Medicine. 1987;**317**(5):265-271. DOI: 10.1056/NEJM198707303170503

[42] Katzav A, Solodeev I, Brodsky O, Chapman J, Pick CG, Blank M, et al. Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. Arthritis and Rheumatism. 2007;**56**(3):938-948. DOI: 10.1002/art.22419

[43] Segovia-Miranda F, Serrano F, Dyrda A, Ampuero E, Retamal C, Bravo-Zehnder M, et al. Pathogenicity of lupus anti-ribosomal P antibodies: Role of cross-reacting neuronal surface P antigen in glutamatergic transmission and plasticity in a mouse model. Arthritis & Rhematology. 2015;**67**(6):1598-1610. DOI: 10.1002/art.39081

[44] Yoshio T, Hirata D, Onda K, Nara H, Minota S. Antiribosomal P protein antibodies in cerebrospinal fluid are associated with neuropsychiatric systemic lupus erythematosus. The Journal of Rheumatology. 2005;**32**(1):34-39

[45] Nery FG, Borba EF, Viana VST, Hatch JP, Soares JC, Bonfá E, et al. Prevalence of depressive and anxiety disorders in systemic lupus erythematosus and their association with anti-ribosomal P antibodies. Progress in Neuro-Psychopharmacology & Biological Psychiatry. 2008;**32**(3):695-700. DOI: 10.1016/j.pnpbp.2007.11.014

[46] Karimifar M, Sharifi I, Shafiey K. Anti-ribosomal P antibodies related to depression in early clinical course of systemic lupus erythematosus. Journal of Research in Medical Sciences. 2013;**18**(10):860-864

[47] Kaichi Y, Kakeda S, Moriya J, Ohnari N, Saito K, Tanaka Y, et al. Brain MR findings in patients with systemic lupus erythematosus with and without antiphospholipid antibody syndrome. American Journal of Neuroradiology. 2014;**35**(1):100-105. DOI: 10.3174/ajnr.A3645

[48] Ezeoke A, Mellor A, Buckley P, Miller B. A systematic, quantitative review of blood autoantibodies in schizophrenia. Schizophrenia Research. 2013;**150**(1):245-251. DOI: 10.1016/J.SCHRES.2013.07.029

[49] Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A, et al. Neuropsychiatric manifestations in systemic lupus erythematosus: Prevalence and association with antiphospholipid antibodies. The Journal of Rheumatology. 2003;**30**(5):985-992. DOI: 0315162X-30-985

[50] Ho RC, Thiaghu C, Ong H, Lu Y, Ho CS, Tam WW, et al. A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus. Autoimmunity Reviews. 2016;**15**:124-138. DOI: 10.1016/j.autrev.2015.10.003

[51] Ziporen L, Polak-Charcon S, Korczyn A, Goldberg I, Afek A, Kopolovic J, et al. Neurological dysfunction associated with antiphospholipid syndrome: Histopathological brain findings of thrombotic changes in a mouse model. Clinical & Developmental Immunology. 2004;**11**(1):67-75. DOI: 10.1080/10446670410001670526

[52] Shoenfeld Y, Nahum A, Dano M, Rabinowitz R, Beilin O, Pick CG,

et al. Neuronal-binding antibodies from patients with antiphospholipid syndrome induce cognitive dee cits following intrathecal passive transfer. Lupus. 2003;**12**:436-442. DOI: 10.1191/0961203303lu409oa

[53] Stojanovich L, Zandman-Goddard G, Pavlovich S, Sikanich N. Psychiatric manifestations in systemic lupus erythematosus. Autoimmunity Reviews. 2007;**6**(6):421-426. DOI: 10.1016/J.AUTREV.2007.02.007

[54] Gerosa M, Poletti B, Pregnolato F, Castellino G, Lafronza A, Silani V, et al. Antiglutamate receptor antibodies and cognitive impairment in primary antiphospholipid syndrome and systemic lupus erythematosus. Frontiers in Immunology. 2016;**7**:5. DOI: 10.3389/fimmu.2016.00005

[55] Sakic B, Kirkham DL, Ballok DA, Mwanjewe J, Fearon IM, Macri J, et al. Proliferating brain cells are a target of neurotoxic CSF in systemic autoimmune disease. Journal of Neuroimmunology. 2005;**169**(1-2):68-85. DOI: 10.1016/j.jneuroim.2005.08.010

[56] Maric D, Millward JM, Ballok DA, Szechtman H, Denburg JA, Barker JL, et al. Neurotoxic properties of cerebrospinal fluid from behaviorally impaired autoimmune mice. Brain Research. 2001;**920**(1-2):183-193. DOI: 10.1016/S0006-8993(01)03060-8

[57] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: When the immune system subjugates the brain. Nature Reviews. Neuroscience. 2008;**9**(1):46-56. DOI: 10.1038/nrn2297

[58] De La Garza R. Endotoxin- or pro-inflammatory cytokine-induced sickness behavior as an animal model of depression: Focus on anhedonia. Neuroscience and Biobehavioral Reviews. 2005;**29**(4-5):761-770. DOI: 10.1016/J.NEUBIOREV.2005.03.016

[59] Simen BB, Duman CH, Simen AA, Duman RS. TNFα signaling in depression and anxiety: Behavioral consequences of individual receptor targeting. Biological Psychiatry. 2006;**59**(9):775-785. DOI: 10.1016/J.BIOPSYCH.2005.10.013

[60] Sakic B, Hanna SE, Millward JM. Behavioral heterogeneity in an animal model of neuropsychiatric lupus. Biological Psychiatry. 2005;**57**(6):679-687. DOI: 10.1016/j.biopsych.2004.11.037

[61] Šakić B, Szechtman H, Braciak T, Richards C, Gauldie J, Denburg JA. Reduced preference for sucrose in autoimmune mice: A possible role of interleukin-6. Brain Research Bulletin. 1997;**44**(2):155-165. DOI: 10.1016/S0361-9230(97)00107-X

[62] Chourbaji S, Urani A, Inta I, Sanchis-Segura C, Brandwein C, Zink M, et al. IL-6 knockout mice exhibit resistance to stress-induced development of depression-like behaviors. Neurobiology of Disease. 2006;**23**(3):587-594. DOI: 10.1016/j.nbd.2006.05.001

[63] Bluthé R-M, Michaud B, Poli V, Dantzer R. Role of IL-6 in cytokine-induced sickness behavior: A study with IL-6 deficient mice. Physiology & Behavior. 2000;**70**(3-4):367-373. DOI: 10.1016/S0031-9384(00)00269-9

[64] Šakić B, Szechtman H, Denburg SD, Denburg JA. Immunosuppressive treatment prevents behavioral deficit in autoimmune MRL-lpr mice. Physiology & Behavior. 1995;**58**(4):797-802. DOI: 10.1016/0031-9384(95)00135-6

[65] Ballok DA, Woulfe J, Sur M, Cyr M, Sakic B. Hippocampal damage in mouse and human forms of systemic autoimmune disease. Hippocampus.

2004;**14**(5):649-661. DOI: 10.1002/hipo.10205

[66] Saija A, Princi P, Lanza M, Scalese M, Aramnejad E, Sarro AD. Systemic cytokine administration can affect blood-brain barrier permeability in the rat. Life Sciences. 1995;**56**(10):775-784. DOI: 10.1016/0024-3205(95)00008-T

[67] Wen J, Xia Y, Stock A, Michaelson JS, Burkly LC, Gulinello M, et al. Neuropsychiatric disease in murine lupus is dependent on the TWEAK/Fn14 pathway. Journal of Autoimmunity. 2013;**43**:44-54. DOI: 10.1016/j.jaut.2013.03.002

[68] Santiago-Raber M-L, Baccala R, Haraldsson KM, Choubey D, Stewart TA, Kono DH, et al. Type-I interferon receptor deficiency reduces lupus-like disease in NZB mice. The Journal of Experimental Medicine. 2003;**197**(6):777-788. DOI: 10.1084/jem.20021996

[69] Jorgensen TN et al. Increased expression of Ifi202, an IFN-activatable gene, in B6.Nba2 lupus susceptible mice inhibits p53-mediated apoptosis. Journal of Immunology. 2006;**176**(10):5863-5870. DOI: 10.4049/jimmunol.176.10.5863

[70] Nickerson KM, Cullen JL, Kashgarian M, Shlomchik MJ. Exacerbated autoimmunity in the absence of TLR9 in MRL.Fas(lpr) mice depends on Ifnar1. Journal of Immunology. 2013;**190**(8):3889-3894. DOI: 10.4049/jimmunol.1203525

[71] Raison CL et al. Neuropsychiatric adverse effects of interferon-α recognition and management. CNS Drugs. 2005;**19**(2):105-123

[72] Capuron L, Miller AH. Cytokines and psychopathology: Lessons from interferon-α. Biological Psychiatry. 2004;**56**(11):819-824. DOI: 10.1016/j.biopsych.2004.02.009

[73] Santer DM, Yoshio T, Minota S, Möller T, Elkon KB. Potent induction of IFN-α and chemokines by autoantibodies in the cerebrospinal fluid of patients with neuropsychiatric lupus. Journal of Immunology. 2009;**182**(2):1192

[74] Bialas AR, Presumey J, Das A, Van Der Poel CE, Lapchak PH, Mesin L, et al. Microglia-dependent synapse loss in type I interferon-mediated lupus. Nature. 2017;**546**(7659):539-543. DOI: 10.1038/nature22821

[75] Dantzer R. Cytokine, sickness behavior, and depression. Immunology and Allergy Clinics of North America. 2009;**29**(2):247-264. DOI: 10.1016/j.iac.2009.02.002

[76] Lemay S, Mao C, Singh AK. Cytokine gene expression in the MRL/lpr model of lupus nephritis. Kidney International. 1996;**50**(1):85-93

[77] Santoro TJ, Benjamin WR, Oppenheim JJ, Steinberg AD. The cellular basis for immune interferon production in autoimmune MRL-Ipr/Ipr mice. Journal of Immunology. 1983;**131**(1):265-268

[78] Tang B, Matsuda T, Akira S, Nagata N, Ikehara S, Hirano T, et al. Age-associated increase in interleukin 6 in MRL/lpr mice. International Immunology. 1991;**3**(3):273-278

[79] Alleva DG, Kaser SB, Beller DI. Aberrant cytokine expression and autocrine regulation characterize macrophages from young MRL+/+ and NZB/W F1 lupus-prone mice. The Journal of Immunology. 1997;**159**:5610-5619

[80] Kothur K, Wienholt L, Brilot F, Dale RC. CSF cytokines/chemokines as biomarkers in neuroinflammatory CNS disorders: A systematic review. Cytokine. 2016;**77**:227-237. DOI: 10.1016/j.cyto.2015.10.001

[81] Goehler LE, Gaykema RP, Nguyen KT, Lee JE, Tilders FJ, Maier SF, et al. Interleukin-1beta in immune cells of the abdominal vagus nerve: A link between the immune and nervous systems? The Journal of Neuroscience. 1999;**19**(7):2799-2806. DOI: 10.1523/JNEUROSCI.19-07-02799.1999

[82] Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: Mechanisms and implications. Trends in Neurosciences. 2002;**25**(3):154-159. DOI: 10.1016/S0166-2236(00)02088-9

[83] Bluthé RM, Walter V, Parnet P, Layé S, Lestage J, Verrier D, et al. Lipopolysaccharide induces sickness behaviour in rats by a vagal mediated mechanism. Comptes Rendus de l'Académie des Sciences—Series III. 1994;**317**(6):499-503

[84] Bluthé RM, Michaud B, Kelley KW, Dantzer R. Vagotomy attenuates behavioural effects of interleukin-1 injected peripherally but not centrally. Neuroreport. 1996;**7**(9):1485-1488

[85] Laye S, Bluthe RM, Kent S, Combe C, Medina C, Parnet P, et al. Subdiaphragmatic vagotomy blocks induction of IL-1 beta mRNA in mice brain in response to peripheral LPS. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 1995;**268**(5):R1327-R1331. DOI: 10.1152/ajpregu.1995.268.5.R1327

[86] Hansen MK, Nguyen KT, Goehler LE, Gaykema RP, Fleshner M, Maier SF, et al. Effects of vagotomy on lipopolysaccharide-induced brain interleukin-1beta protein in rats. Autonomic Neuroscience. 2000;**85**(1-3):119-126

[87] Hosoi T, Okuma Y, Nomura Y. Electrical stimulation of afferent vagus nerve induces IL-1β expression in the brain and activates HPA axis. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 2000;**279**(1):R141-R147. DOI: 10.1152/ajpregu.2000.279.1.R141

[88] van Dam A-M, Brouns M, Louisse S, Berkenbosch F. Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: A pathway for the induction of non-specific symptoms of sickness? Brain Research. 1992;**588**(2):291-296. DOI: 10.1016/0006-8993(92)91588-6

[89] Konsman JP, Kelley K, Dantzer R. Temporal and spatial relationships between lipopolysaccharide-induced expression of Fos, interleukin-1beta and inducible nitric oxide synthase in rat brain. Neuroscience. 1999;**89**(2):535-548

[90] Giunti D, Parodi B, Cordano C, Uccelli A, Kerlero de Rosbo N. Can we switch microglia's phenotype to foster neuroprotection? Focus on multiple sclerosis. Immunology. 2014;**141**(3): 328-339. DOI: 10.1111/imm.12177

[91] Cunningham MA, Wirth JR, Freeman LR, Boger HA, Granholm A-C, Gilkeson GS. Estrogen receptor alpha deficiency protects against development of cognitive impairment in murine lupus. Journal of Neuroinflammation. 2014;**11**:171. DOI: 10.1186/s12974-014-0171-x

[92] The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis & Rheumatology. 1999;**42**(4):599-608. DOI: 10.1002/1529-0131(199904)42:4<599::AID-ANR2>3.0.CO;2-F

[93] Joseph FG, Scolding NJ. Neurolupus. Practical Neurology. 2010;**10**(1):4-15. DOI: 10.1136/jnnp.2009.200071

[94] Tay SH, Mak A. Diagnosing and attributing neuropsychiatric events to systemic lupus erythematosus: Time to

untie the Gordian knot? Rheumatology 2016;**56**(suppl_1):kew338. DOI: 10.1093/rheumatology/kew338

[95] Ainiala H, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsänoja R, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: A population-based evaluation. Arthritis and Rheumatism. 2001;**45**(5):419-423. DOI: 10.1002/1529-0131(200110)45:5<419::AID-ART360>3.0.CO;2-X

[96] Unterman A, Nolte JES, Boaz M, Abady M, Shoenfeld Y, Zandman-Goddard G. Neuropsychiatric syndromes in systemic lupus erythematosus: A meta-analysis. Seminars in Arthritis and Rheumatism. 2011;**41**(1):1-11. DOI: 10.1016/J.SEMARTHRIT.2010.08.001

[97] Jeltsch-David H, Muller S. Neuropsychiatric systemic lupus erythematosus: Pathogenesis and biomarkers [Internet]. Nature Reviews Neurology. 2014;**10**:579-596. DOI: 10.1038/nrneurol.2014.148

[98] Zandman-Goddard G, Chapman J, Shoenfeld Y. Autoantibodies involved in neuropsychiatric SLE and antiphospholipid syndrome. Seminars in Arthritis and Rheumatism. 2007;**36**(5):297-315. DOI: 10.1016/j.semarthrit.2006.11.003

[99] Lai N-S, Lan J-L. Evaluation of cerebrospinal anticardiolipin antibodies in lupus patients with neuropsychiatric manifestations. Lupus. 2000;**9**:353-357

[100] Julian LJ, Tonner C, Yelin E, Yazdany J, Trupin L, Criswell LA, et al. Cardiovascular and disease-related predictors of depression in systemic lupus erythematosus. Arthritis Care & Research (Hoboken). 2011;**63**(4):542-549. DOI: 10.1002/acr.20426

[101] Murray SG, Yazdany J, Kaiser R, Criswell LA, Trupin L, Yelin EH, et al. Cardiovascular disease and cognitive dysfunction in systemic lupus erythematosus. Arthritis Care & Research (Hoboken). 2012;**64**(9):1328-1333. DOI: 10.1002/acr.21691

[102] Roman MJ, Shanker B-A, Davis A, Lockshin MD, Sammaritano L, Simantov R, et al. Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. The New England Journal of Medicine. 2003;**349**(25):2399-2406. DOI: 10.1056/NEJMoa035471

[103] Salmon JE, Roman MJ. Subclinical atherosclerosis in rheumatoid arthritis and systemic lupus erythematosus. The American Journal of Medicine. 2008;**121**(10 Suppl.1):3-8. DOI: 10.1016/j.amjmed.2008.06.010

[104] Tektonidou MG, Kravvariti E, Konstantonis G, Tentolouris N, Sfikakis PP, Protogerou A. Subclinical atherosclerosis in systemic lupus erythematosus: Comparable risk with diabetes mellitus and rheumatoid arthritis. 2017. DOI: 10.1016/j.autrev.2017.01.009

[105] Tomietto P, Annese V, D'agostini S, Venturini P, La Torre G, De Vita S, et al. General and specific factors associated with severity of cognitive impairment in systemic lupus erythematosus. Arthritis and Rheumatism. 2007;**57**(8):1461-1472. DOI: 10.1002/art.23098

[106] Hanly JG, Urowitz MB, Su L, Gordon C, Bae SC, Sanchez-Guerrero J, et al. Seizure disorders in systemic lupus erythematosus results from an international, prospective, inception cohort study. Annals of the Rheumatic Diseases. 2012;**71**(9):1502-1509. DOI: 10.1136/annrheumdis-2011-201089

[107] Jolly M, Mikolaitis RA, Shakoor N, Fogg LF, Block JA, Katz P. Education, zip code-based annualized household income, and health outcomes in patients with systemic lupus erythematosus.

The Journal of Rheumatology. 2010;**37**(6):1150-1157. DOI: 10.3899/jrheum.090862

[108] Ward MM. Education level and mortality in systemic lupus erythematosus (SLE): Evidence of underascertainment of deaths due to SLE in ethnic minorities with low education levels. Arthritis Care & Research (Hoboken). 2004;**51**(4): 616-624. DOI: 10.1002/art.20526

[109] Andrade RM, Alarcón GS, González LA, Fernández M, Apte M, Vilá LM, et al. Seizures in patients with systemic lupus erythematosus: Data from LUMINA, a multiethnic cohort (LUMINA LIV). Annals of the Rheumatic Diseases. 2008;**67**(6):829-834. DOI: 10.1136/ard.2007.077594

[110] Hanly JG, Urowitz MB, Su L, Bae SC, Gordon C, Wallace DJ, et al. Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. Annals of the Rheumatic Diseases. 2010;**69**(3):529-535. DOI: 10.1136/ard.2008.106351

[111] Mikdashi J, Krumholz A, Handwerger B. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. Neurology. 2005;**64**(12):2102-2107. DOI: 10.1212/01.WNL.0000165959.98370.D5

[112] Mackworth-Young C, Hughes G. Epilepsy: an early symptom of systemic lupus erythematosus. Journal of Neurology, Neurosurgery, and Psychiatry. 1985;**48**:185-192

[113] González-Duarte A, Cantú-Brito CG, Ruano-Calderón L, García-Ramos G. Clinical description of seizures in patients with systemic lupus erythematosus. European Neurology. 2008;**59**(6):320-323. DOI: 10.1159/000121423

[114] Appenzeller S, Cendes F, Costallat LT. Epileptic seizures in systemic lupus erythematosus. Neurology. 2004;**63**(10):1808-1812. DOI: 10.1212/01.WNL.0000144178.32208.4F

[115] Liou HH, Wang CR, Chou HC, Arvanov VL, Chen RC, Chang YC, et al. Anticardiolipin antisera from lupus patients with seizures reduce a GABA receptor-mediated chloride current in snail neurons. Life Sciences. 1994;**54**(15):1119-1125. DOI: 10.1016/0024-3205(94)00422-6

[116] Chapman J, Cohen-Armon M, Shoenfeld Y, Korczyn A. Antiphospholipid antibodies permeabilize and depolarize brain synaptoneurosomes

[117] Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Coté R, et al. Seizures after stroke. Archives of Neurology. 2000;**57**(11):1617. DOI: 10.1001/archneur.57.11.1617

[118] Alarcón GS, McGwin G, Bertoli AM, Fessler BJ, Calvo-Alén J, Bastian HM, et al. Effect of hydroxychloroquine on the survival of patients with systemic lupus erythematosus: Data from LUMINA, a multiethnic US cohort (LUMINA L). Annals of the Rheumatic Diseases. 2007;**66**(9):1168-1172. DOI: 10.1136/ard.2006.068676

[119] Lund JM, Alexopoulou L, Sato A, Karow M, Adams NC, Gale NW, et al. Recognition of single-stranded RNA viruses by Toll-like receptor 7. Proceedings of the National Academy of Sciences of the United States of America. 2004;**101**(15):5598-5603. DOI: 10.1073/pnas.0400937101

[120] Rutz M, Metzger J, Gellert T, Luppa P, Lipford GB, Wagner H, et al. Toll-like receptor 9 binds single-stranded CpG-DNA in a sequence- and pH-dependent manner. European Journal of

Immunology. 2004;**34**(9):2541-2550. DOI: 10.1002/eji.200425218

[121] Tam LS, Gladman DD, Hallett DC, Rahman P, Urowitz MB. Effect of antimalarial agents on the fasting lipid profile in systemic lupus erythematosus. The Journal of Rheumatology. 2000;**27**(9):2142-2145

[122] Borba EF, Bonfá E. Longterm beneficial effect of chloroquine diphosphate on lipoprotein profile in lupus patients with and without steroid therapy. The Journal of Rheumatology. 2001;**28**(4):780-785

[123] Sachet JC, Borba EF, Bonfá E, Vinagre C, Silva VM, Maranhão RC. Chloroquine increases low-density lipoprotein removal from plasma in systemic lupus patients. Lupus. 2007;**16**:273-278. DOI: 10.1177/0961203307077579

[124] Misita CP. Hydroxychloroquine reverses thrombogenic properties of antiphospholipid antibodies in mice. Circulation. 2005;**112**(3):e39-e44. DOI: 10.1161/CIRCULATIONAHA.105.548495

[125] Ruiz-Irastorza G, Egurbide M-V, Pijoan J-I, Garmendia M, Villar I, Martinez-Berriotxoa A, et al. Effect of antimalarials on thrombosis and survival in patients with systemic lupus erythematosus. Lupus. 2006;**15**:577-583. DOI: 10.1177/0961203306071872

[126] Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: Results from a large, multi-ethnic cohort. Annals of the Rheumatic Diseases. 2009;**68**(2):238-241. DOI: 10.1136/ard.2008.093013

[127] Li X-Y, Xiao H-B, Pai P. Myelitis in systemic lupus erythematosus. Journal of Clinical Neuroscience. 2017;**44**:18-22. DOI: 10.1016/J.JOCN.2017.06.003

[128] Birnbaum J, Petri M, Thompson R, Izbudak I, Kerr D. Distinct subtypes of myelitis in systemic lupus erythematosus. Arthritis and Rheumatism. 2009;**60**(11):3378-3387. DOI: 10.1002/art.24937

[129] D'Cruz DP, Mellor-Pita S, Joven B, Sanna G, Allanson J, Taylor J, et al. Transverse myelitis as the first manifestation of systemic lupus erythematosus or lupus-like disease: Good functional outcome and relevance of antiphospholipid antibodies. The Journal of Rheumatology. 2004;**31**(2):280-285

[130] Kovacs B, Laverty TL, Brent LH, Dehoratius RJ. Transverse myelopathy in systemic lupus erythematosus: An analysis of 14 cases and review of the literature. Annals of the Rheumatic Diseases. 2000;**59**:120-124

[131] Magro-Checa C, Zirkzee EJ, Huizinga TW, Steup-Beekman GM. Management of neuropsychiatric systemic lupus erythematosus: Current approaches and future perspectives. Drugs. 2016;**76**(4):459-483. DOI: 10.1007/s40265-015-0534-3

[132] Mok CC, Lau CS, Chan EY, Wong RW. Acute transverse myelopathy in systemic lupus erythematosus: Clinical presentation, treatment, and outcome. The Journal of Rheumatology. 1998;**25**(3):467-473

[133] Lu X, Gu Y, Wang Y, Chen S, Ye S. Prognostic factors of lupus myelopathy. Lupus. 2008;**17**:323-328. DOI: 10.1177/0961203307088005

[134] Magro Checa C, Cohen D, Bollen ELEM, Van Buchem MA, Huizinga TWJ, Steup-Beekman GM. Demyelinating disease in SLE: Is it multiple sclerosis or lupus? Best Practice & Research Clinical Rheumatology. 2013;**27**:405-424. DOI: 10.1016/j.berh.2013.07.010

[135] Katsiari CG, Giavri I, Mitsikostas DD, Yiannopoulou KG, Sfikakis PP. Acute transverse myelitis and antiphospholipid antibodies in lupus. No evidence for anticoagulation. European Journal of Neurology. 2011;**18**(4):556-563. DOI: 10.1111/j.1468-1331.2010.03208.x

[136] Miller DH, Chard DT, Ciccarelli O. Clinically isolated syndromes. Lancet Neurology. 2012;**11**(2):157-169. DOI: 10.1016/S1474-4422(11)70274-5

[137] Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: A review of neuropathologic findings in 57 cases, 1955-1977. Seminars in Arthritis and Rheumatism. 1979;**8**(3):212-221. DOI: 10.1016/S0049-0172(79)80009-8

[138] Theodoridou A, Settas L. Demyelination in rheumatic diseases. Journal of Neurology, Neurosurgery, and Psychiatry. 2006;**77**(3):290-295. DOI: 10.1136/jnnp.2005.075861

[139] Miller D, Weinshenker B, Filippi M, Banwell B, Cohen J, Freedman M, et al. Differential diagnosis of suspected multiple sclerosis: A consensus approach. Multiple Sclerosis. 2008;**14**:1157-1174. DOI: 10.1177/1352458508096878

[140] IJdo JW, Conti-Kelly AM, Greco P, Abedi M, Amos M, Provenzale JM, et al. Anti-phospholipid antibodies in patients with multiple sclerosis and MS-like illnesses: MS or APS? Lupus. 1999;**8**(2):109-115. DOI: 10.1191/096120399678847461

[141] Cuadrado MJ, Khamashta MA, Ballesteros A, Godfrey T, Simon MJ, Hughes GR. Can neurologic manifestations of Hughes (antiphospholipid) syndrome be distinguished from multiple sclerosis? Analysis of 27 patients and review of the literature. Medicine (Baltimore). 2000;**79**(1):57-68

[142] Feng X, Reder NP, Yanamandala M, Hill A, Franek BS, Niewold TB, et al. Type I interferon signature is high in lupus and neuromyelitis optica but low in multiple sclerosis. Journal of the Neurological Sciences. 2012;**313**:48-53. DOI: 10.1016/j.jns.2011.09.032

[143] Madsen C. The innovative development in interferon beta treatments of relapsing-remitting multiple sclerosis. Brain and Behavior: A Cognitive Neuroscience Perspective. 2017;**7**(6):e00696. DOI: 10.1002/brb3.696

[144] Bertsias GK, Ioannidis JPA, Aringer M, Bollen E, Bombardieri S, Bruce IN, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: Report of a task force of the EULAR standing committee for clinical affairs. Annals of the Rheumatic Diseases. 2010;**69**(12):2074-2082. DOI: 10.1136/ard.2010.130476

[145] Jarius S, Paul F, Franciotta D, Waters P, Zipp F, Hohlfeld R, et al. Mechanisms of disease: Aquaporin-4 antibodies in neuromyelitis optica. Nature Clinical Practice. Neurology. 2008;**4**(4):202-214. DOI: 10.1038/ncpneuro0764

[146] Kovacs KT, Kalluri SR, Boza-Serrano A, Deierborg T, Csepany T, Simo M, et al. Change in autoantibody and cytokine responses during the evolution of neuromyelitis optica in patients with systemic lupus erythematosus: A preliminary study. Multiple Sclerosis. 2016;**22**(9):1192-1201. DOI: 10.1177/1352458515613165

[147] Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: Distinction from multiple sclerosis.

Lancet. 2004;**364**(9451):2106-2112. DOI: 10.1016/S0140-6736(04)17551-X

[148] Chapman J. The interface of multiple sclerosis and antiphospholipid antibodies. Thrombosis Research. 2004;**114**(5-6):477-481. DOI: 10.1016/j.thromres.2004.06.016

[149] Stepień M, Cendrowski W. Form of systemic lupus erythematosus (lupoid sclerosis) resembling multiple sclerosis. Neurologia i Neurochirurgia Polska. 1974;**8**(4):607-609

[150] Harris EN, Gharavi AE, Mackworth-Young CG, Patel BM, Derue G, Hughes GR. Lupoid sclerosis: A possible pathogenetic role for antiphospholipid antibodies. Annals of the Rheumatic Diseases. 1985;**44**(4):281-283

[151] Kinnunen E, Müller K, Keto P, Ketonen L, Helve T, Sepponen R. Cerebrospinal fluid and MRI findings in three patients with multiple sclerosis and systemic lupus erythematosus. Acta Neurologica Scandinavica. 1993;**87**(5):356-360

[152] Zenone T, Steineur MP, Sibille M, Durieu I, Vital Durand D. Myelopathy revealing lupus. Two cases and review of the literature. La Revue de Médecine Interne. 2000;**21**(12):1114-1120

[153] Piga M, Chessa E, Peltz MT, Floris A, Mathieu A, Cauli A. Demyelinating syndrome in SLE encompasses different subtypes: Do we need new classification criteria? Pooled results from systematic literature review and monocentric cohort analysis. Autoimmunity Reviews. 2017;**16**(3):244-252. DOI: 10.1016/J.AUTREV.2017.01.011

[154] Wallace DJ, Metzger AL, Klinenberg JR. NSAID usage patterns by rheumatologists in the treatment of SLE. The Journal of Rheumatology. 1989;**16**(4):557-560

[155] Morís G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis revisited. JAMA Internal Medicine. 2014;**174**(9):1511. DOI: 10.1001/jamainternmed.2014.2918

[156] Kozora E, Ellison MC, West AS. Reliability and validity of the proposed American College of Rheumatology neuropsychological battery for systemic lupus erythematosus. Arthritis & Rheumatism. 2004;**51**(5):810-818. DOI: 10.1002/art.20692

[157] Nagai M, Hoshide S, Ishikawa J, Shimada K, Kario K. Ambulatory blood pressure as an independent determinant of brain atrophy and cognitive function in elderly hypertension. Journal of Hypertension. 2008;**26**(8):1636-1641. DOI: 10.1097/HJH.0b013e3283018333

[158] Patel MD, Coshall C, Rudd AG, Wolfe CD. Cognitive impairment after stroke: Clinical determinants and its associations with long-term stroke outcomes. Journal of the American Geriatrics Society. 2002;**50**:700-706

[159] Nery FG, Borba EF, Hatch JP, Soares JC, Bonfá E, Neto FL. Major depressive disorder and disease activity in systemic lupus erythematosus. Comprehensive Psychiatry. 2007;**48**:14-19. DOI: 10.1016/j.comppsych.2006.04.002

[160] Sehlo MG, Bahlas SM. Perceived illness stigma is associated with depression in female patients with systemic lupus erythematosus. Journal of Psychosomatic Research. 2013;**74**:248-251. DOI: 10.1016/j.jpsychores.2012.09.023

[161] Nishimura K, Omori M, Sato E, Katsumata Y, Gono T, Kawaguchi Y, et al. New-onset psychiatric disorders after corticosteroid therapy in systemic lupus erythematosus: An observational case-series study. Journal of Neurology.

2014;**261**(11):2150-2158. DOI: 10.1007/s00415-014-7472-y

[162] Bhangle SD, Kramer N, Rosenstein ED. Corticosteroid-induced neuropsychiatric disorders: Review and contrast with neuropsychiatric lupus. Rheumatology International. 2013;**33**(8):1923-1932. DOI: 10.1007/s00296-013-2750-z

[163] Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. Psychoneuroendocrinology. 1996;**21**(1):25-31

[164] Brown ES. Effects of glucocorticoids on mood, memory, and the hippocampus. Annals of the New York Academy of Sciences. 2009;**1179**(1):41-55. DOI: 10.1111/j.1749-6632.2009.04981.x

[165] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders [Internet]. American Psychiatric Association; Arlington, VA. 2013. DOI: 10.1176/appi.books.9780890425596

[166] Pego-reigosa JM, Isenberg DA. Psychosis due to systemic lupus erythematosus: Characteristics and long-term outcome of this rare manifestation of the disease. Rheumatology. 2008;**47**(10):1498-1502. DOI: 10.1093/rheumatology/ken260

[167] Ainiala H, Loukkola J, Peltola J, Korpela M, Hietaharju A. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. Neurology. 2001;**57**(3):496-500. DOI: 10.1212/WNL.57.3.496

[168] Brey RL, Holliday SL, Saklad AR, Navarrete MG, Hermosillo-Romo D, Stallworth CL, et al. Neuropsychiatric syndromes in lupus: Prevalence using standardized definitions. Neurology. 2002;**58**(8):1214-1220. DOI: 10.1212/WNL.58.8.1214

[169] Hanly JG, Mccurdy G, Fougere L, Douglas J-A, Thompson K, Hanly JG. Neuropsychiatric events in systemic lupus erythematosus: Attribution and clinical neuropsychiatric events in systemic lupus erythematosus: Attribution and clinical significance. Journal of Rheumatology. 2004;**3131**(31):2156-2162

[170] Diagnostic and Statistical Manual of Mental Disorders. 4th ed. American Psychiatric Association. Washington, DC: American Psychiatric Association; 1994

[171] Appenzeller S, Cendes F, Costallat LTL. Acute psychosis in systemic lupus erythematosus. Rheumatology International. 2008;**28**(3):237-243. DOI: 10.1007/s00296-007-0410-x

[172] Postal M, Costallat LTL, Appenzeller S. Neuropsychiatric manifestations in systemic lupus erythematosus epidemiology, pathophysiology and management. CNS Drugs. 2011;**25**(9):721-736. DOI: 1172-7047/11/0009-0721

[173] Hanly JG, Harrison MJ. Management of neuropsychiatric lupus. Best Practice & Research. Clinical Rheumatology. 2005;**19**(5):799-821. DOI: 10.1016/J.BERH.2005.04.003

[174] Pamfil C, Fanouriakis A, Damian L, Rinzis M, Sidiropoulos P, Tsivgoulis G, et al. EULAR recommendations for neuropsychiatric systemic lupus erythematosus *vs* usual care: Results from two European centres. Rheumatology. 2015;**54**(7):1270-1278. DOI: 10.1093/rheumatology/keu482

[175] Mitsikostas DD, Sfikakis PP, Goadsby PJ. A meta-analysis for headache in systemic lupus erythematosus: The evidence and the

myth. Brain. 2004;**127**(5):1200-1209. DOI: 10.1093/brain/awh146

[176] Davey R, Bamford J, Emery P. The ACR classification criteria for headache disorders in SLE fail to classify certain prevalent headache types. Cephalalgia. 2008;**28**(3):296-299. DOI: 10.1111/j.1468-2982.2007.01510.x

[177] Hanly JG, Urowitz MB, O'Keeffe AG, Gordon C, Bae S-C, Sanchez-Guerrero J, et al. Headache in systemic lupus erythematosus: Results from a prospective, international inception cohort study. Arthritis and Rheumatism. 2013;**65**(11):2887-2897. DOI: 10.1002/art.38106

[178] Mok CC, To CH, Mak A. Neuropsychiatric damage in southern Chinese patients with systemic lupus erythematosus. Medicine (Baltimore). 2006;**85**(4):221-228. DOI: 10.1097/01.md.0000231955.08350.1b

[179] Briani C, Lucchetta M, Ghirardello A, Toffanin E, Zampieri S, Ruggero S, et al. Neurolupus is associated with anti-ribosomal P protein antibodies: An inception cohort study. Journal of Autoimmunity. 2009;**32**(2):79-84. DOI: 10.1016/J.JAUT.2008.12.002

[180] Zirkzee EJM, Steup-Beekman GM, van der Mast RC, Bollen ELEM, van der Wee NJA, Baptist E, et al. Prospective study of clinical phenotypes in neuropsychiatric systemic lupus erythematosus; multidisciplinary approach to diagnosis and therapy. The Journal of Rheumatology. 2012;**39**(11):2118-2126. DOI: 10.3899/jrheum.120545

[181] Buttgereit F, da Silva JAP, Boers M, Burmester G-R, Cutolo M, Jacobs J, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: Current questions and tentative answers in rheumatology. Annals of the Rheumatic Diseases. 2002;**61**(8):718-722

[182] Zonana-Nacach A, Barr SG, Magder LS, Petri M. Damage in systemic lupus erythematosus and its association with corticosteroids. Arthritis and Rheumatism. 2000;**43**(8):1801-1808. DOI: 10.1002/1529-0131(200008)43:8<1801::AID-ANR16>3.0.CO;2-O

[183] Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, Medina J-A, Moran M-A, Ruiz-Irastorza G. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. Rheumatology. 2014;**53**(8):1470-1476. DOI: 10.1093/rheumatology/keu148

[184] Barile-Fabris L, Ariza-Andraca R, Olguín-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limón JM, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Annals of the Rheumatic Diseases. 2005;**64**(4):620-625. DOI: 10.1136/ard.2004.025528

[185] Fernandes Moça Trevisani V, Castro AA, Ferreira Neves Neto J, Atallah ÁN. Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. Cochrane Database of Systematic Reviews. 2013;**2**:CD002265. DOI: 10.1002/14651858.CD002265.pub3

[186] Harrison MJ, Morris KA, Horton R, Toglia J, Barsky J, Chait S, et al. Results of intervention for lupus patients with self-perceived cognitive difficulties. Neurology. 2005;**65**(8):1325-1327. DOI: 10.1212/01.wnl.0000180938.69146.5e

[187] Haupt M, Millen S, Jänner M, Falagan D, Fischer-Betz R, Schneider M. Improvement of coping abilities in patients with systemic lupus erythematosus: A prospective study. Annals of the Rheumatic Diseases. 2005;**64**(11):1618-1623. DOI: 10.1136/ard.2004.029926

[188] Petri M. Use of hydroxychloroquine to prevent thrombosis in systemic lupus erythematosus and in antiphospholipid antibody—Positive patients. Current Rheumatology Reports. 2011;**13**(1):77-80. DOI: 10.1007/s11926-010-0141-y

[189] Akhavan PS, Su J, Lou W, Gladman DD, Urowitz MB, Fortin PR. The early protective effect of hydroxychloroquine on the risk of cumulative damage in patients with systemic lupus erythematosus. The Journal of Rheumatology. 2013;**40**(6):831-841. DOI: 10.3899/jrheum.120572

[190] Shinjo SK, Bonfá E, Wojdyla D, Borba EF, Ramirez LA, Scherbarth HR, et al. Antimalarial treatment may have a time-dependent effect on lupus survival: Data from a multinational Latin American inception cohort. Arthritis and Rheumatism. 2010;**62**(3):855-862. DOI: 10.1002/art.27300

[191] Profumo E, Buttari B, Saso L, Rigano R. Pleiotropic effects of statins in atherosclerotic disease: Focus on the antioxidant activity of atorvastatin. Current Topics in Medicinal Chemistry. 2014;**14**(22):2542-2551

[192] Petri MA, Kiani AN, Post W, Christopher-Stine L, Magder LS. Lupus atherosclerosis prevention study (LAPS). Annals of the Rheumatic Diseases. 2011;**70**(5):760-765. DOI: 10.1136/ard.2010.136762

[193] Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, Brey R, Crowther M, Derksen R, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. Lupus. 2011;**20**:206-218. DOI: 10.1177/0961203310395803

[194] Cuadrado MJ, Bertolaccini ML, Seed PT, Tektonidou MG, Aguirre A, Mico L, et al. Low-dose aspirin vs low-dose aspirin plus low-intensity warfarin in thromboprophylaxis: A prospective, multicentre, randomized, open, controlled trial in patients positive for antiphospholipid antibodies (ALIWAPAS). Rheumatology. 2014;**53**(2):275-284. DOI: 10.1093/rheumatology/ket313

[195] Andrade D, Cervera R, Cohen H, Crowther M, Cuadrado MJ, Canaud G, et al. 15th International Congress on antiphospholipid antibodies task force on antiphospholipid syndrome treatment trends report. In: Antiphospholipid Syndrome. Cham: Springer International Publishing; 2017. pp. 317-338. DOI: 10.1007/978-3-319-55442-6_18

[196] Mathian A, Hie M, Cohen-Aubart F, Amoura Z. Targeting interferons in systemic lupus erythematosus: Current and future prospects. Drugs. 2015;**75**(8):835-846. DOI: 10.1007/s40265-015-0394-x

[197] Baccala R, Gonzalez-Quintial R, Schreiber RD, Lawson BR, Kono DH, Theofilopoulos AN. Anti-IFN-/receptor antibody treatment ameliorates disease in lupus-predisposed mice. Journal of Immunology. 2012;**189**(12):5976-5984. DOI: 10.4049/jimmunol.1201477

[198] Shiozawa S, Kuroki Y, Kim M, Hirohata S, Ogino T. Interferon-alpha in lupus psychosis. Arthritis and Rheumatism. 1992;**35**(4):417-422. DOI: 10.1002/art.1780350410

[199] Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an anti-interferon-a receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. Arthritis & Rhematology. 2017;**69**(2):376-386. DOI: 10.1002/art.39962

Edited by Sophia Lionaki

Systemic lupus erythematosus, the prototype of an autoimmune disorder, may affect several organs and may run a chronic course between relapse and remission. This book covers important aspects of the disease, including epidemiology, pathophysiology, and neuropsychiatric manifestations, including basic science and clinical features and management. In affected patients, the fundamental problem of fertility is reassessed including the risk of the disease, the possibility of fetal loss, the safety of drugs during pregnancy, and the current diagnostic and suggested therapeutic strategies of reproductive medicine. Finally, the issue of pathogenesis is revisited with a thorough description of animal models in relation to physiology and potential novel therapies.

Published in London, UK

IntechOpen

ISBN 978-1-83880-184-7