

2019 update of the EULAR recommendations for the management of systemic lupus erythematosus

Fanouriakis, Antonis; Gordon, Caroline

DOI:

[10.1136/annrheumdis-2019-215089](https://doi.org/10.1136/annrheumdis-2019-215089)

License:

None: All rights reserved

Document Version

Peer reviewed version

Citation for published version (Harvard):

Fanouriakis, A & Gordon, C 2019, '2019 update of the EULAR recommendations for the management of systemic lupus erythematosus', *Annals of the Rheumatic Diseases*, vol. 78, no. 6, pp. 736-745.
<https://doi.org/10.1136/annrheumdis-2019-215089>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Checked for eligibility: 04/04/2019

This article has been accepted for publication in *Annals of the Rheumatic Diseases*, 2019 following peer review, and the Version of Record can be accessed online at [10.1136/annrheumdis-2019-215089](https://doi.org/10.1136/annrheumdis-2019-215089)

Copyright information: © Author(s) (or their employer(s)) 2019. No commercial re-use. See rights and permissions. Published by BMJ.

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

2019 update of the EULAR recommendations for the management of systemic lupus erythematosus

Antonis Fanouriakis^{1*}, Myrto Kostopoulou², Alessia Alunno³, Martin Aringer⁴, Ingeborg Bajema⁵, John N. Boletis⁶, Ricard Cervera⁷, Andrea Doria⁸, Caroline Gordon⁹, Marcello Govoni¹⁰, Frederic Houssiau¹¹, David Jayne¹², Marios Kouloumas¹³, Annegret Kuhn¹⁴, Janni L. Larsen¹⁵, Kirsten Lerstrom¹⁶, Gabriela Moroni¹⁷, Marta Mosca¹⁸, Matthias Schneider¹⁹, Josef S. Smolen²⁰, Elisabet Svenungsson²¹, Vladimir Tesar²², Angela Tincani²³, Anne Troldborg²⁴, Ronald van Vollenhoven²⁵, Jörg Wenzel²⁶, George Bertsias^{27**}, Dimitrios T. Boumpas^{1,28,29**}

¹ *Rheumatology and Clinical Immunology Unit, "Attikon" University Hospital, Athens, Greece*

² *Department of Nephrology, "G. Gennimatas" General Hospital, Athens, Greece*

³ *Rheumatology Unit, Department of Medicine, University of Perugia, Perugia, Italy*

⁴ *Division of Rheumatology, Department of Medicine III, University Medical Center & Faculty of Medicine Carl Gustav Carus at the TU Dresden, Dresden, Germany*

⁵ *Department of Pathology, Leiden University Medical Center, Leiden, Netherlands*

⁶ *Nephrology Department and Renal Transplantation Unit, "Laikon" Hospital, National and Kapodistrian University of Athens, Medical School, Athens, Greece*

⁷ *Department of Autoimmune Diseases, Hospital Clinic, Barcelona, Spain*

⁸ *Rheumatology Unit, Department of Medicine, University of Padova, Padova, Italy*

⁹ *Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom*

¹⁰ *Department of Medical Sciences, Section of Rheumatology, University of Ferrara, Azienda Ospedaliero-Universitaria Sant'Anna Ferrara, Italy*

¹¹ *Cliniques Universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium*

- ¹² *Department of Medicine, Cambridge, Cambridge, United Kingdom*
- ¹³ *Cyprus League Against Rheumatism, Aglantzia, Cyprus*
- ¹⁴ *University Hospital Muenster, Muenster, Germany*
- ¹⁵ *Copenhagen Lupus and Vasculitis Clinic, Rheumatology and Spine Diseases Centre, Rigshospitalet, Copenhagen, Denmark*
- ¹⁶ *Lupus Europe, Farum, Denmark*
- ¹⁷ *Nephrology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan*
- ¹⁸ *Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy*
- ¹⁹ *Department of Rheumatology & Hiller Research Unit Rheumatology, UKD, Heinrich-Heine University, Düsseldorf, Germany*
- ²⁰ *Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria*
- ²¹ *Department of Medicine, Rheumatology Unit, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden*
- ²² *Department of Nephrology, 1st Faculty of Medicine and General University Hospital, Charles University, Prague, Czech Republic*
- ²³ *Rheumatology and Clinical Immunology, University of Brescia, Brescia, Italy*
- ²⁴ *Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark*
- ²⁵ *Department of Rheumatology and Clinical Immunology, Amsterdam University Medical Centers, Amsterdam, The Netherlands*
- ²⁶ *Department of Dermatology and Allergy, University Hospital Bonn, Germany*
- ²⁷ *Rheumatology, Clinical Immunology and Allergy, University Hospital of Heraklion, Greece*
- ²⁸ *Laboratory of Autoimmunity and Inflammation, Biomedical Research Foundation of the Academy of Athens, Athens, Greece*

²⁹ *Joint Academic Rheumatology Program, Medical School, National and Kapodestrian University of Athens, Athens, Greece and Medical School, University of Cyprus, Nicosia, Cyprus*

** Antonis Fanouriakis was supported by an Articulum Fellowship and a grant from the Hellenic Society of Rheumatology during the completion of this work*

*** These authors contributed equally to this work*

Corresponding author: Dimitrios Boumpas, MD, FACP

Professor of Medicine

National and Kapodestrian University of Athens

12462 Athens, Greece

Tel.: (+30) 210 5831990

E-mail: boumpasd@uoc.gr

Word count: 3612

Abstract

Objectives: To update the EULAR recommendations for the management of systemic lupus erythematosus (SLE) based upon emerging new evidence.

Methods: Systematic literature review (01/2007-12/2017) followed by modified Delphi method to form questions, elicit expert opinions and reach consensus.

Results: Treatment in SLE aims at remission or low disease activity and prevention of flares. Hydroxychloroquine is recommended in all lupus patients, at a dose not exceeding 5mg/kg real body weight. During chronic maintenance treatment, glucocorticoids should be minimized to less than 7.5 mg/day (prednisone equivalent) and, when possible, withdrawn. Appropriate initiation of immunomodulatory agents (methotrexate, azathioprine, mycophenolate) can expedite the tapering/discontinuation of glucocorticoids. In persistently active or flaring extrarenal disease, add-on belimumab should be considered; rituximab may be considered in organ-threatening, refractory disease. Updated specific recommendations are also provided for cutaneous, neuropsychiatric, haematological and renal disease. SLE patients should be assessed for their antiphospholipid antibody status, infectious and cardiovascular diseases risk profile, and preventative strategies be tailored accordingly.

Conclusion: The recommendations provide physicians and patients with updated consensus guidance on the management of SLE, combining evidence-base and expert-opinion.

Keywords: Systemic lupus erythematosus, treatment, lupus nephritis

Introduction

Systemic lupus erythematosus (SLE) has variable presentation, course and prognosis. The wide acceptance and popularity of the first EULAR recommendations for its management, published in 2008,¹ prompted the subsequent development of specific recommendations regarding monitoring, neuropsychiatric and renal disease, as well as for pregnancy and women's health in lupus.²⁻⁵ Since these publications, new data have emerged on treatment strategies and validated goals of treatment, alternative regimens of glucocorticoids (GC), "multitargeted" therapy with the use of calcineurin inhibitors (CNIs) in lupus nephritis (LN), and the approval of the first biologic therapy for SLE. These advances called for an update of the EULAR recommendations for lupus, capitalizing on the strengths of and experience from the previous projects.⁶

Methods

After approval by the EULAR Executive Committee, the convenor (DB) and methodologist (GB) invited a Task Force to work on this update; two fellows (AF, MK) undertook the systematic literature review (SLR). The EULAR standardised operating procedures⁷ and the Appraisal of Guidelines Research and Evaluation instrument (AGREE II)⁸ were followed. Applying a Delphi-based methodology, 14 research questions were selected for SLR (**Supplementary Table 1**). PubMed was screened using strings of relevant terms. Since this was an update of the previous 2007 recommendations, the SLR considered all English-language publications from 01/2007 until 12/2017, *with two exceptions*: i) treatment of skin disease, wherein an unrestricted date search was performed, and ii) renal disease, wherein search was limited to the period 01/2012 – 12/2017 (since the EULAR recommendations for LN were published in 2012). Pertinent articles, identified by manual search within the reference list of the originally retrieved publications, were also included. All retrieved items were refined based on article type, abstract, full-text content and number of included patients. The final level of evidence and grading of recommendations considered also the body of evidence that had informed the previous sets of EULAR recommendations for the management of SLE, as the convenor, methodologist and several of the panellists had also participated in the latter. A detailed presentation of the SLR results is given in **Supplementary Tables 2 and 3**. Evidence was categorised based on the design and validity of available studies and the strength of the statements was graded (see

Supplementary Table 4). After rounds of discussions, the committee reached a consensus of 33 final statements, grouped in 4 broad categories (Goals of Treatment, Treatment of SLE, Specific manifestations, Comorbidities - **Table 1**). Each Task Force member rated their agreement with each statement.

Table 1. Recommendations for the management of patients with systemic lupus erythematosus

Overarching principles	
<ul style="list-style-type: none"> SLE is a multisystem disease - occasionally limited to one or few organs - diagnosed on clinical grounds in the presence of characteristic serologic abnormalities. 	
<ul style="list-style-type: none"> SLE care is multidisciplinary, based on a shared patient-physician decision, and should consider individual, medical and societal costs. 	
<ul style="list-style-type: none"> Treatment of organ-/life-threatening SLE includes an initial period of high-intensity immunosuppressive therapy to control disease activity, followed by a longer period of less intensive therapy to consolidate response and prevent relapses. 	
<ul style="list-style-type: none"> Treatment goals include long-term patient survival, prevention of organ damage and optimization of health-related quality of life. 	
Recommendation/Statement	Level of agreement, mean (SD)
1. Goals of treatment	
1.1 Treatment in SLE should aim at remission or low disease activity (2b/B) and prevention of flares (2b/B) in all organs, maintained with the lowest possible dose of glucocorticoids.	10.0 (0)
1.2 Flares of SLE can be treated according to the severity of organ(s) involvement by adjusting ongoing therapies (glucocorticoids, immunomodulating agents) to higher doses, switching, or adding new therapies (2b/C).	9.95 (0.22)
2. Treatment of SLE	
2.1 Hydroxychloroquine (HCQ)	
2.1.1 HCQ is recommended for all patients with SLE (1b/A), unless contraindicated, at a dose not exceeding 5 mg/kg/real BW (3b/C).	9.65 (1.11)
2.1.2 In the absence of risk factors for retinal toxicity, ophthalmologic screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be	9.75 (0.70)

performed at baseline, after 5 years, and yearly thereafter (2b/B).	
2.2 Glucocorticoids (GC)	
2.2.1 GC can be used at doses and route of administration that depend on the type and severity of organ involvement (2b/C).	9.95 (0.22)
2.2.2 Pulses of intravenous methylprednisolone (usually 250–1000 mg per day, for 1–3 days) provide immediate therapeutic effect and enable the use of lower starting dose of oral GC (3b/C).	9.85 (0.36)
2.2.3 For chronic maintenance treatment, GC should be minimized to less than 7.5 mg/day (prednisone equivalent) (1b/B) and, when possible, withdrawn.	9.65 (0.65)
2.2.4 Prompt initiation of immunomodulatory agents can expedite the tapering/discontinuation of GC (2b/B).	9.90 (0.30)
2.3 Immunosuppressive therapies	
2.3.1 In patients not responding to HCQ (alone or in combination with GC) or patients unable to reduce GC below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents such as methotrexate , (1b/B) azathioprine (2b/C) or mycophenolate (2a/B) should be considered.	9.85 (0.48)
2.3.2 Immunomodulating/immunosuppressive agents can be included in the initial therapy in cases of organ-threatening disease (2b/C).	9.85 (0.48)
2.3.3 Cyclophosphamide can be used for severe organ- or life-threatening SLE as well as “rescue” therapy in patients not responding to other immunosuppressive agents (2b/C).	9.90 (0.30)
2.4 Biologics	
2.4.1 In patients with inadequate response to standard-of-care (combinations of HCQ and GC with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of glucocorticoids and/or frequent relapses, add-on treatment with belimumab should be considered (1a/A).	9.20 (0.81)
2.4.2 In organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents, rituximab can be considered (2b/C).	9.85 (0.48)
3 Specific manifestations	
3.1 Skin disease	
3.1.1 First-line treatment of skin disease in SLE includes topical agents (GC, calcineurin inhibitors) (2b/B), antimalarials (HCQ, quinacrine) (1a/A) and/or systemic GC (4/C).	10.0 (0)
3.1.2 In non-responsive cases or cases requiring high-dose GC, methotrexate (3a/B), retinoids (4/C), dapsone (4/C) or mycophenolate (4/C) can be added.	9.85 (0.48)

3.2 Neuropsychiatric disease	
3.2.1 Attribution to SLE - as opposed to non-SLE - related neuropsychiatric manifestations, is essential and can be facilitated by neuroimaging, investigation of cerebrospinal fluid, consideration of risk factors [type and timing of the manifestation in relation to the onset of lupus, patient age, non-neurological lupus activity, presence of antiphospholipid antibodies (aPL)] and exclusion of confounding factors (2b/C).	9.65 (0.85)
3.2.2 Treatment of SLE-related neuropsychiatric disease includes glucocorticoids/immunosuppressive agents for manifestations considered to reflect an inflammatory process (1b/A), and antiplatelet/anticoagulants for atherothrombotic/aPL-related manifestations (2b/C).	9.85 (0.48)
3.3 Hematologic disease	
3.3.1 Acute treatment of lupus thrombocytopenia includes high-dose GC (including pulses of intravenous methylprednisolone) (4/C) and/or intravenous immunoglobulin G (4/C).	9.95 (0.22)
3.3.2 For maintenance of response, immunosuppressive/GC-sparing agents such as mycophenolate (2b/C) , azathioprine (2b/C) , or cyclosporine (4/C) can be used.	9.75 (0.62)
3.3.3 Refractory cases can be treated with rituximab (3a/C) or cyclophosphamide (4/C) .	9.65 (0.73)
3.4 Renal disease	
3.4.1 Early recognition of signs of renal involvement and - when present - performance of a diagnostic renal biopsy are essential to ensure optimal outcomes (2b/B).	9.95 (0.22)
3.4.2 Mycophenolate (1a/A) or low-dose IV cyclophosphamide (2a/B) are recommended as initial (induction) treatment, as they have the best efficacy/toxicity ratio.	9.85 (0.36)
3.4.3 In patients at high risk for renal failure (reduced glomerular filtration rate, histologic presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis], similar regimens may be considered but high-dose IV cyclophosphamide can also be used (1b/A).	9.45 (0.80)
3.4.4 For maintenance therapy, mycophenolate (1a/A) or azathioprine (1a/A) should be used.	9.75 (0.62)
3.4.5 In cases with stable/improved renal function but incomplete renal response (persistent proteinuria >0.8-1 g/24h after at least one year of immunosuppressive treatment), repeat biopsy can distinguish chronic from active kidney lesions (4/C).	9.85 (0.48)
3.4.6 Mycophenolate may be combined with low dose of a calcineurin inhibitor in severe	9.50 (0.81)

nephrotic syndrome (2b/C) or incomplete renal response (4/C), in the absence of uncontrolled hypertension, high chronicity index at kidney biopsy and/or reduced GFR.	
4 Comorbidities	
4.1 Antiphospholipid syndrome	
4.1.1 All SLE patients should be screened at diagnosis for aPL (1a/A).	10.0 (0)
4.1.2 SLE patients with high-risk aPL profile (persistently positive medium/high titres or multiple positivity) may receive primary prophylaxis with antiplatelet agents (2a/C), especially if other atherosclerotic/thrombophilic factors are present, after balancing the bleeding hazard.	9.45 (0.80)
4.1.3 For secondary prevention (thrombosis, pregnancy complication/loss), the therapeutic approach should be the same as for primary anti-phospholipid syndrome (1b/B).	10.0 (0)
4.2 Infectious diseases	
4.2.1 SLE patients should be assessed for general and disease-related risk factors for infections, such as advanced age/frailty (-/D), diabetes mellitus (-/D), renal involvement (2b/B), immunosuppressive/biologic therapy (1b-2b/B-C) and use of GC (1a/A).	9.85 (0.65)
4.2.2 General preventative measures (including immunizations) and early recognition and treatment of infection/sepsis are recommended (-/D).	9.90 (0.44)
4.3 Cardiovascular disease	
4.3.1 Patients with SLE should undergo regular assessment for traditional (1b/B-C) and disease-related risk factors for cardiovascular disease, including persistently active disease (1b/B), increased disease duration (1b/A), medium/high titres of aPL (1b/A), renal involvement (1b/B) (especially, persistent proteinuria and/or GFR <60 ml/min) and chronic use of GC (1b/B).	9.85 (0.65)
4.3.2 Based on their individual cardiovascular risk profile, SLE patients may be candidates for preventative strategies as in the general population, including low-dose aspirin (2b/D) and/or lipid-lowering agents (2b/D) .	9.85 (0.48)

Results and Discussion

Overarching principles

SLE represents a challenge for the treating physician in terms of diagnosis and treatment. Its protean manifestations, often multisystem but occasionally limited to a few or single organ, have led some physicians to focus exclusively on evidence of serologic autoimmunity [antinuclear (ANA) and more specific autoantibodies], for a disease where diagnosis is clinical after excluding competing diagnoses. Monitoring of SLE through validated disease activity and chronicity indices, including physician global assessment (PGA), is recommended. For patients with severe disease, multidisciplinary care in dedicated lupus centres is desirable.⁹ Immunosuppressive (IS) therapy (for induction and maintenance of remission) is indicated in organ-threatening lupus.

Recommendations

Goals of treatment

To improve long-term patient outcomes, management should aim at remission of disease symptoms and signs, prevention of damage accrual and minimisation of drug side-effects, as well as improvement of quality of life.^{10,11} *Complete remission* (absence of clinical activity with no use of GC and IS drugs) is infrequent.¹²⁻¹⁶ To this end, newly defined low disease activity states (based on a SLEDAI score ≤ 3 on antimalarials, or alternatively SLEDAI ≤ 4 , PGA ≤ 1 with GC ≤ 7.5 mg of prednisone and well tolerated IS agents) have shown comparable rates with remission, regarding halting of damage accrual (OR 0.5-0.7 for increase in damage index) and prevention of flares.^{14,17-20} Accordingly, treatment in SLE should aim at remission or, if this state cannot be achieved, at low disease activity in all organ systems. In lupus nephritis (LN), therapy should aim at least *partial remission* [defined as $\geq 50\%$ reduction in proteinuria (UPr) to subnephrotic levels and serum creatinine (SCr) within 10% from baseline] by 6-12 months; *complete renal remission* (proteinuria < 500 mg/24hr and SCr within 10% from baseline), however, may require longer treatment duration, often more than 12 and until 24 months. In monitoring renal response, reduction of UPr (to less than 0.8 gm/d) following treatment is more important than residual haematuria.²¹ Patients with more

severe proteinuria and longer-standing disease are less likely to respond or show more delayed responses.^{22,23}

Prevention of disease flares is an additional milestone of SLE treatment. Although a universally accepted definition is lacking, most experts agree that a flare is a measurable increase in disease activity usually leading to change of treatment.²⁴ Flares are common in the disease course and contribute significantly to organ damage accrual and worse outcome.^{17,25,26} Consistently reported risk factors for a higher disease flare rate include younger age at disease onset, no use of antimalarials, persistent generalized disease activity and serologic activity (anti-dsDNA, low complement).²⁷⁻³¹ Assessment of adherence to drug treatment, close monitoring and optimisation of disease control in these patients may reduce the risk for a flare.

Treatment of SLE

i) Hydroxychloroquine

Hydroxychloroquine (HCQ) is recommended for all patients with SLE. There is evidence for multiple beneficial effects of HCQ in SLE,³² yet poor adherence to treatment is not uncommon.³³⁻³⁵ Drug blood levels can be used to assess compliance,^{33,35} but data are currently insufficient to recommend routine monitoring of drug levels. Concerns for retinal toxicity with long-term HCQ therapy led to the use of more sensitive screening techniques, with a prevalence of retinal abnormalities exceeding 10% after 20 years of continuous use.^{36,37} Major risk factors for retinopathy include duration of treatment (OR 4.71 for every 5 years of use), dose (OR 3.34 for every 100 mg daily dose), chronic kidney disease (adjusted OR 8.56) and preexisting retinal or macular disease.³⁷ Based on existing evidence suggesting that the risk of toxicity is very low for doses below 5 mg/Kg real body weight, the daily dose should not exceed this threshold. Of note, efficacy of HCQ in lupus has been established in studies with a prescribed dose of 6.5 mg/Kg/day, thus it remains to be confirmed whether a lower dose will have comparable clinical effects. Patients in long-standing remission may have their dose lowered, although no studies have formally addressed this strategy. The choice of quinacrine, an alternative antimalarial, can be considered in patients with cutaneous manifestations and HCQ-induced retinal toxicity.

ii) Glucocorticoids

GC can provide rapid symptom relief, but the medium to long-term aim should be to minimize daily dose to ≤ 7.5 mg/day prednisone equivalent or to discontinue them, because long-term GC therapy can have various detrimental effects including irreversible organ damage.³⁸⁻⁴¹ Risks are substantially increased at continuous GC doses above 7.5 mg/day, with some studies suggesting that also lower doses might be harmful.^{17,42-44} To this end, two approaches can be considered: i) use of pulses of intravenous methylprednisolone (IV MP) of various doses (depending on severity and body weight), which take advantage of the rapid non-genomic effects of GC⁴⁵ and may allow for a lower starting dose and faster tapering of PO GC^{46,47}, and ii) early initiation of immunosuppressive agents, to facilitate tapering and eventual discontinuation of oral GC (*see below*). High-dose IV MP (usually 250 to 1000 mg/day for 3 days) is often used in acute, organ-threatening disease (e.g. renal, neuropsychiatric) after excluding infections.⁴⁸

iii) *Immunosuppressive (IS) drugs*

Consequent initiation of IS drugs facilitates a more rapid GC tapering and may prevent disease flares.⁴⁹ The choice of agent depends on prevailing disease manifestation(s), patient age and childbearing potential, safety concerns and cost. Methotrexate (MTX) and azathioprine (AZA) should be considered in patients with poor symptom control after a trial with GC and HCQ or when HCQ alone is unlikely to be sufficient, due to the large experience gained with their use and their relatively safe profile.⁵⁰ Published evidence is generally stronger for MTX than AZA, yet the latter is compatible with pregnancy contemplation. Mycophenolate mofetil (MMF) is a potent immunosuppressant with efficacy in renal and non-renal lupus (although not in neuropsychiatric disease).⁵¹⁻⁵³ In a recent randomized, open-label trial in extrarenal SLE, enteric-coated mycophenolate sodium (EC-MPS) was superior to AZA in achieving remission and reducing flares.⁵⁴ However, its teratogenic potential (needs to be discontinued at least 6 weeks before conceiving), along with its higher cost compared to AZA or MTX, poses a limitation towards universal recommendation in women of reproductive age with non-renal manifestations. Cyclophosphamide (CYC) can be considered in organ-threatening disease (especially renal, cardiopulmonary or neuropsychiatric) and only as rescue therapy in refractory non-major organ manifestations; due to its gonadotoxic effects, it should be used with caution in women and men of fertile age.⁵⁵⁻⁵⁷ Concomitant use of GnRH analogs attenuates the depletion of ovarian reserve associated with CYC therapy and is recommended in premenopausal SLE patients.^{4,58,59} Information

about the possibility of ovarian cryopreservation should be offered ahead of treatment. Other risks of CYC therapy such as malignancy and infections should also be considered.^{60,61}

iv) *Biologic agents*

There is evidence to support beneficial effects of B-cell targeting agents in SLE.⁶²⁻⁶⁶ Belimumab should be considered in extrarenal disease with inadequate control (ongoing disease activity or frequent flares) to first-line treatments (typically including combination of HCQ and prednisone with or without IS agents), and inability to taper GC daily dose to acceptable levels (i.e. maximum 7.5 mg/day). Patients with persistent disease may benefit from belimumab; more likely to respond are patients with high disease activity (e.g. SLEDAI >10), prednisone dose >7.5 mg/day and serologic activity (low C3/C4, high anti-dsDNA titres), with cutaneous, musculoskeletal and serologic manifestations responding the most.⁶⁷⁻⁶⁹

Due to the negative results of randomized controlled trials (RCT), rituximab (RTX) is currently only used off-label, in patients with severe renal or extrarenal (mainly hematological and neuropsychiatric) disease refractory to other IS agents and/or belimumab, or in patients with contraindications to these drugs. As a general rule, more than one IS drug need to have failed prior to RTX administration,⁷⁰⁻⁷³ except perhaps for cases of severe autoimmune thrombocytopenia and hemolytic anemia, wherein RTX has demonstrated efficacy both in lupus and in patients with isolated immune thrombocytopenia (ITP).⁷⁴⁻⁷⁶ In lupus nephritis, RTX is typically considered following failure of first-line therapies (CYC, MMF) or in relapsing disease.^{70,77} More recently, a *post hoc* analysis of the LUNAR trial showed that complete B-cell depletion following RTX treatment in LN was associated with higher odds for complete response at 78 weeks.⁷⁸

Figure 1 summarizes the various drugs used in the treatment of SLE, according to disease severity stratification. **Supplementary Table 5** outlines the recommended doses of the drugs mentioned in the manuscript.

Specific manifestations

i) Skin disease

A large body of evidence originates from studies in patients with cutaneous lupus erythematosus (CLE). Effective protection from ultraviolet exposure with broad-spectrum sunscreens and smoking cessation are

strongly recommended.⁷⁹⁻⁸¹ In atypical or refractory cases, a diagnostic skin biopsy should be considered. First line treatment of skin disease includes topical agents (GC and/or calcineurin inhibitors) and antimalarials, with or without systemic GC (the latter at a starting dose depending on severity of skin involvement).^{82,83} HCQ is the antimalarial of choice over chloroquine due to its multiple beneficial effects and possibly lower risk for retinal toxicity;⁸⁴ in cases of inadequate response or evidence of toxic retinopathy, quinacrine (mepacrine) may be used as an add-on or sequential therapy, respectively.⁸⁵⁻⁸⁷ Albeit quinacrine is currently unavailable in several countries worldwide, it is a useful alternative when available. There are no studies examining retinal toxicity of quinacrine with the newer, more sensitive screening techniques (visual fields or optical coherence tomography), however with current knowledge, retinopathy is not considered a side-effect of quinacrine.

A sizeable proportion (almost 40%) of patients will not respond to first-line treatment.^{86,88} In such cases, MTX can be added.^{50,89} Other agents include retinoids, dapsone and MMF or EC-mycophenolic acid^{79,90,91}. Belimumab and RTX have also shown efficacy in mucocutaneous manifestations of SLE, although these studies have not included a validated activity score for skin lesions; RTX may be less efficacious in chronic forms of skin lupus.^{62,92-94} Thalidomide is effective in various subtypes of cutaneous disease.^{95,96} Due to its strict contraindication in pregnancy, the risk for irreversible polyneuropathy, and the frequent relapses upon drug discontinuation, it should be considered only as a “rescue” therapy in patients who have failed multiple previous agents. A treatment algorithm for the various subtypes of cutaneous lupus erythematosus has been published by a European group of Dermatologists guided by the European Dermatology Forum in cooperation with the European Academy of Dermatology and Venereology. [79]

ii) Neuropsychiatric disease (NPSLE)

Attribution of neuropsychiatric manifestations to SLE often requires a comprehensive, multidisciplinary approach to rule out mimics (infections, malignancy and others), taking into account the presence of risk (“favoring”) factors [type and timing of manifestation, presence of generalized, non-neurological disease activity, abnormal neuroimaging and cerebrospinal fluid analysis, positive antiphospholipid antibodies (aPL)],⁹⁷ as well as confounding factors favoring alternative diagnoses.⁹⁸ The use of validated attribution models may aid in the diagnostic process.^{99,100}

Treatment of NPSLE depends on whether the underlying pathophysiologic mechanism is presumed to be inflammatory or embolic/thrombotic/ischemic.^{2,101} GC and/or IS agents should be considered in the former, while anticoagulant/antithrombotic treatment is favored when aPL antibodies are present.¹⁰²⁻¹⁰⁷ Distinction between the two pathophysiologic processes may not be easy in clinical practice, or the two processes may coexist in the same patient.² Combination of IS and anticoagulant/antithrombotic therapy may be considered in these patients. SLE patients with cerebrovascular disease should be managed like the general population in the acute phase; in addition to controlling extra-CNS lupus activity, IS therapy may be considered in the absence of aPL antibodies and other atherosclerotic risk factors or in recurrent cerebrovascular events.¹⁰⁸ In this context, neuroimaging and/or CSF studies may provide additional supporting evidence for immunosuppressive therapy. Targeted symptomatic therapy is indicated according to the type of manifestation (eg. antipsychotics for psychosis, anxiolytics for anxiety disorder etc).

ii) Haematological disease

Haematological manifestations frequently necessitating anti-inflammatory/immunosuppressive treatment in SLE patients include thrombocytopenia and autoimmune hemolytic anemia (AIHA). First-line treatment of significant lupus thrombocytopenia (platelet count below 30,000/mm³) consists of moderate/high doses of GC in combination with IS agent (AZA, MMF or cyclosporine; the latter having the least potential for myelotoxicity) to facilitate GC-sparing. Initial therapy with pulses of IV MP (1 to 3 days) is encouraged. Intravenous immunoglobulin (IVIG) may be considered in the acute phase, in cases of inadequate response to high-dose GC or to avoid GC-related infectious complications.

Treatment of thrombocytopenia is typically lengthy and often characterized by relapses during GC tapering.¹⁰⁹ In patients with no response to GC (i.e. failure to reach a platelet count > 50,000/mm³) or relapses, RTX should be considered, considering also its efficacy in ITP.^{74,76,110} CYC may also be considered in such cases. Thrombopoietin agonists or splenectomy should be reserved as last options.^{111,112} Autoimmune hemolytic anemia (AIHA) is far less common than thrombocytopenia in SLE; its treatment follows the same principles regarding use of GC, IS drugs and RTX. Autoimmune leukopenia is common in SLE but rarely needs treatment; careful work-up is recommended to exclude other causes of leukopenia (especially drug-induced).

iv) Renal disease

Patients at high risk of developing renal involvement (males, juvenile lupus onset, serologically active including positivity for anti-C1q antibodies)¹¹³⁻¹¹⁵ should be under vigilant monitoring (e.g. at least every 3 months) to detect early signs of kidney disease. Following diagnosis, secured with a kidney biopsy, treatment of LN includes an initial induction phase, followed by a more prolonged maintenance phase. MMF and CYC are the IS agents of choice for induction treatment; low-dose CYC (Euro-Lupus regimen, **Supplementary Table S5**) is preferred over high-dose CYC as it has comparable efficacy and lower risk of gonadotoxicity.^{57,116,117} Published data support the use of MMF and high-dose CYC (**Supplementary Table S5**) in severe forms of LN associated with increased risk of progression into end-stage renal disease (ESRD) [reduced glomerular filtration rate (GFR), histologic presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis].^{118,119} An early significant drop in UPr (to ≤ 1 gr/day at 6 months or ≤ 0.8 gr/day at 12 months) is a predictor of favorable long-term renal outcome.^{21,117,120} MMF or AZA may be used as maintenance therapy, with the former associated with fewer relapses;^{121,122} the choice depends on the agent used for induction phase and on patient characteristics, including age, race and wish for pregnancy. In refractory or relapsing disease, RTX may be considered.

Following the EULAR recommendations for LN in 2012, several studies have been published regarding the use of calcineurin inhibitors (CNIs) to treat proliferative LN, either alone or in the form of a “multitarget therapy” (combination of tacrolimus with MMF).¹²³⁻¹²⁷ These studies were performed almost exclusively in Asian populations and had short follow-up hence data have to be corroborated with longer duration studies in multiethnic populations. To this end, at present, CNIs may be considered as second-line agents for induction or maintenance therapy mainly in membranous LN, podocytopathy, or in proliferative disease with refractory nephrotic syndrome, despite standard-of-care within 3-6 months,^{128,129} in the latter case, they may be used alone or in combination with MMF, since small, observational studies have shown the CNI/MMF combination to be effective in disease refractory to standard therapy.¹³⁰⁻¹³² Monitoring SCr and blood levels of CNI to avoid chronic drug toxicity is essential.

Comorbidities

i) Antiphospholipid antibodies (aPL) and Antiphospholipid syndrome (APS)

The presence of aPL is associated with thrombotic and obstetric complications, and increased risk of damage accrual.^{133,134} In aPL carriers, a recent meta-analysis supported a protective role of low-dose aspirin for primary prophylaxis against thrombosis in the subgroup of aPL carriers who had SLE,¹³⁵ however, in view of the potential bleeding hazard,^{136,137} it is not clear whether this should be applied to lupus patients with any aPL antibodies or only to those carrying a high risk aPL profile (ie. triple aPL positivity, lupus anticoagulant or high titers of anti-cardiolipin antibodies).¹³⁸ SLE patients with aPL may also receive additional anticoagulant treatment, such as low-molecular weight heparin, during high-risk periods for thrombosis (pregnancy or postoperatively), although no studies have formally addressed this question.

No studies have been performed exclusively on SLE-APS patients, with several studies excluding secondary APS due to lupus. Thus, with current knowledge, treatment of APS in the context of SLE should not differ from treatment of primary APS. A recent randomized, open-label trial comparing rivaroxaban to warfarin in APS with triple aPL positivity (~21% of patients had SLE-APS) was prematurely terminated due to an excess of thromboembolic events in the rivaroxaban arm.¹³⁹ Thus, in patients with SLE-APS, use of novel oral anticoagulants for secondary prevention should be avoided; however, they could potentially serve as an alternative option in selected patients (low-risk aPL profile, no history of arterial thrombotic events) with difficult to control international normalized ratio on warfarin, after balancing possible risks.

ii) Infections

Risk of infection in SLE is associated with both disease-related and treatment-related factors; high-dose GC therapy, CYC, MMF and RTX are all associated with an increased risk for infection, while high disease activity, severe leukopenia and presence of renal involvement (\pm hypogammaglobulinemia in nephrotic syndrome) also contribute independently.^{48,140-143} Protection against infections should be proactive, focusing both on primary prevention, as well as timely recognition and treatment. Lupus patients should receive vaccinations according to the EULAR recommendations for vaccination of patients with autoimmune rheumatic diseases.^{144,145} Immunization against seasonal influenza and pneumococcal infection (both PCV13 and PPSV23) should be strongly considered, preferably during stable disease. Herpes zoster vaccination is now available for the general population, but a study in SLE has not been performed. Prompt diagnosis and

treatment of sepsis is essential. To this end, validated scores such as the quick SOFA [(systolic blood pressure ≤ 100 mmHg, respiratory rate ≥ 22 /min, altered mental state with Glasgow coma scale < 15): the presence of ≥ 2 points near the onset of infection is associated with a greater risk of death or prolonged intensive care unit stay] may identify patients who are at greater risk for a poor outcome.¹⁴⁶

iii) Cardiovascular disease

SLE is an independent risk factor for cardiovascular disease (CVD), due to both traditional and disease-related risk factors, such as persistent disease activity, LN, presence of aPL and use of GC.¹⁴⁷⁻¹⁴⁹ Surrogate measures of atherosclerosis, such as carotid plaques, carotid intima media thickness (cIMT) and coronary artery calcium (CAC) are frequently used to identify subclinical CVD in SLE.¹⁵⁰ Low-dose aspirin may be considered for primary prevention of CVD, as it may reduce the risk for incident CVD in SLE (HR 0.24 in one retrospective study).^{151,152} However, this has to be viewed in light of recent large studies in diabetics and elderly showing that the benefits of aspirin for primary CVD prevention are counterbalanced by the larger bleeding hazard.^{136,153} The value of statins in SLE has been tested in RCTs, which failed to show a clear benefit over placebo, when cIMT was used a surrogate marker for CVD.^{154,155} Thus, routine use of statins is not recommended for all patients but should be considered on the basis of lipid levels and the presence of other traditional risk factors. Calculation of the 10-year CVD risk using the Systematic Coronary Risk Evaluation (SCORE, <https://www.escardio.org/Education/Practice-Tools/CVD-prevention-toolbox/SCORE-Risk-Charts>) is recommended,¹⁵⁶ although the actual risk is underestimated in patients with SLE.

Certain points to consider and the research agenda suggested by the Task Force Members are reported in **Table 2**. These points aim to improve the design of clinical studies in order to answer clinically important questions, for which the current “state-of-the-art” is insufficient. In particular, data regarding the optimal duration and timing of discontinuation of therapy in both renal and extrarenal disease are scarce,¹⁵⁷ for the former, recent studies support the value of a repeat kidney biopsy for the management of maintenance therapy, but more data are needed.^{158,159}

Table 2. Future research agenda in SLE

Targets of therapy

- Exploration of a universally accepted level of residual disease activity, if remission cannot be achieved

Existing therapies and disease monitoring

- Efficacy of CNI-containing treatment regimens in LN in different racial/ethnic groups and at longer time points
- Usefulness of measurements of drug blood levels (HCQ, MMF etc)
- Efficacy of quinacrine as immunomodulator in patients with HCQ-induced retinal toxicity.
- Comparative trials of conventional IS drugs with global and organ-specific result reporting
- Randomized trials testing lower cumulative dose glucocorticoid regimens versus conventional regimens
- Optimal treatment regimen of RTX: Regular versus on-demand
- Optimal duration of therapy and timing of discontinuation (renal and extrarenal disease)
- Value of repeat kidney biopsy for monitoring LN and determination of clinical versus histologic response to therapy

Pathophysiology and Biomarkers

- Susceptibility to develop SLE
- Involvement of particular organ systems over others, multisystem versus organ-dominant disease
- Response to specific therapeutic agents over others (pharmacogenetics, transcriptomics etc)

Clinical trial design and new drug development

- Optimization of clinical trial design and study endpoints to maximize probability of new drug approval in SLE
- Handling of background medication to avoid polypharmacy and “dilution” of positive effects of drugs under study
- Inclusion of organ-specific endpoints and disease activity measures
- Increase in number of adequately trained trial sites (recruitment, infrastructure and training)
- Academia versus industry-driven clinical trials

Acknowledgments: The committee wishes to acknowledge the support of the EULAR Standing Committee on Clinical Affairs. The committee also expresses its sincere appreciation and gratitude to the EULAR Secretariat and especially to Patrizia Jud, executive assistant, for the outstanding organisation.

Funding: European League against Rheumatism

Competing interests: To be provided

Figure 1. Treatment of non-renal SLE – Recommended drugs with respective grading of recommendation

aPL: Antiphospholipid antibodies; HCQ: Hydroxychloroquine; GC: Glucocorticoids; PO: Per os; IM: Intramuscular; IV: Intravenous; MTX: Methotrexate; AZA: Azathioprine; BEL: Belimumab; CNI: Calcineurin inhibitors; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; RTX: Rituximab; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; Pre: Prednisone

References

1. Bertsias G, Ioannidis JP, Boletis J, et al. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. *Ann Rheum Dis* 2008;67(2):195-205.
2. Bertsias GK, Ioannidis JP, Aringer M, 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. *Ann Rheum Dis* 2010;69(12):2074-82.
3. Bertsias GK, Tektonidou M, Amoura Z, et al. Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. *Ann Rheum Dis* 2012;71(11):1771-82.
4. 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. *Ann Rheum Dis* 2017;76(3):476-85.
5. Mosca M, Tani C, Aringer M, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. *Ann Rheum Dis* 2010;69(7):1269-74.
6. Boumpas DT, Bertsias GK, Fanouriakis A. 2008-2018: a decade of recommendations for systemic lupus erythematosus. *Ann Rheum Dis* 2018;77(11):1547-8.
7. van der Heijde D, Aletaha D, Carmona L, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74(1):8-13.
8. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182(18):E839-42.
9. Ward MM. Hospital experience and mortality in patients with systemic lupus erythematosus. *Arthritis Rheum* 1999;42(5):891-8.

10. van Vollenhoven R, Voskuyl A, Bertsias G, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis* 2017;76(3):554-61.
11. van Vollenhoven RF, Mosca M, Bertsias G, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;73(6):958-67.
12. Medina-Quinones CV, Ramos-Merino L, Ruiz-Sada P, et al. Analysis of Complete Remission in Systemic Lupus Erythematosus Patients Over a 32-Year Period. *Arthritis Care Res (Hoboken)* 2016;68(7):981-7.
13. Steiman AJ, Urowitz MB, Ibanez D, et al. Prolonged clinical remission in patients with systemic lupus erythematosus. *J Rheumatol* 2014;41(9):1808-16.
14. Ugarte-Gil MF, Wojdyla D, Pons-Estel GJ, et al. Remission and Low Disease Activity Status (LDAS) protect lupus patients from damage occurrence: data from a multiethnic, multinational Latin American Lupus Cohort (GLADEL). *Ann Rheum Dis* 2017;76(12):2071-4.
15. Urowitz MB, Feletar M, Bruce IN, et al. Prolonged remission in systemic lupus erythematosus. *J Rheumatol* 2005;32(8):1467-72.
16. Zen M, Iaccarino L, Gatto M, et al. Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Ann Rheum Dis* 2015;74(12):2117-22.
17. Tsang ASMW, Bultink IE, Heslinga M, et al. Both prolonged remission and Lupus Low Disease Activity State are associated with reduced damage accrual in systemic lupus erythematosus. *Rheumatology (Oxford)* 2017;56(1):121-8.
18. Zen M, Iaccarino L, Gatto M, et al. Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Ann Rheum Dis* 2018;77(1):104-10.
19. Polachek A, Gladman DD, Su J, et al. Defining Low Disease Activity in Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)* 2017;69(7):997-1003.
20. Tselios K, Gladman DD, Touma Z, et al. Clinical remission and low disease activity have comparable outcomes over 10 years in systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2018 Jul 28. doi: 10.1002/acr.23720.

21. Dall'Era M, Cisternas MG, Smilek DE, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. *Arthritis Rheumatol* 2015;67(5):1305-13.
22. Touma Z, Urowitz MB, Ibanez D, et al. Time to recovery from proteinuria in patients with lupus nephritis receiving standard treatment. *J Rheumatol* 2014;41(4):688-97.
23. Mackay M, Dall'Era M, Fishbein J, et al. Establishing Surrogate Kidney Endpoints for Lupus Nephritis Clinical Trials: Development and Validation of a Novel Approach to Predict Future Kidney Outcomes. *Arthritis Rheumatol* 2018 Sep 17. doi: 10.1002/art.40724.
24. Ruperto N, Hanrahan LM, Alarcon GS, et al. International consensus for a definition of disease flare in lupus. *Lupus* 2011;20(5):453-62.
25. Koutsonikoli A, Trachana M, Heidich AB, et al. Dissecting the damage in Northern Greek patients with childhood-onset systemic lupus erythematosus: a retrospective cohort study. *Rheumatol Int* 2015;35(7):1225-32.
26. Ugarte-Gil MF, Acevedo-Vasquez E, Alarcon GS, et al. The number of flares patients experience impacts on damage accrual in systemic lupus erythematosus: data from a multiethnic Latin American cohort. *Ann Rheum Dis* 2014;74(6):1019-23.
27. Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis* 2016;75(9):1615-21.
28. Kasitanon N, Intaniwet T, Wangkaew S, et al. The clinically quiescent phase in early-diagnosed SLE patients: inception cohort study. *Rheumatology (Oxford)* 2015;54(5):868-75.
29. Petri MA, van Vollenhoven RF, Buyon J, et al. Baseline predictors of systemic lupus erythematosus flares: data from the combined placebo groups in the phase III belimumab trials. *Arthritis Rheum* 2013;65(8):2143-53.
30. Steiman AJ, Gladman DD, Ibanez D, et al. Outcomes in patients with systemic lupus erythematosus with and without a prolonged serologically active clinically quiescent period. *Arthritis Care Res (Hoboken)* 2012;64(4):511-8.
31. Weiss JE, Sison CP, Ilowite NT, et al. Flares in pediatric systemic lupus erythematosus. *J Rheumatol* 2007;34(6):1341-4.

32. Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P, et al. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. *Ann Rheum Dis* 2010;69(1):20-8.
33. Costedoat-Chalumeau N, Amoura Z, Hulot JS, et al. Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. *Ann Rheum Dis* 2007;66(6):821-4.
34. Iudici M, Pantano I, Fasano S, et al. Health status and concomitant prescription of immunosuppressants are risk factors for hydroxychloroquine non-adherence in systemic lupus patients with prolonged inactive disease. *Lupus* 2018;27(2):265-72.
35. Mok CC, Penn HJ, Chan KL, et al. Hydroxychloroquine Serum Concentrations and Flares of Systemic Lupus Erythematosus: A Longitudinal Cohort Analysis. *Arthritis Care Res (Hoboken)* 2016;68(9):1295-302.
36. Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014;132(12):1453-60.
37. Kim JW, Kim YY, Lee H, et al. Risk of Retinal Toxicity in Longterm Users of Hydroxychloroquine. *J Rheumatol* 2017;44(11):1674-9.
38. Bruce IN, O'Keefe AG, Farewell V, et al. Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. *Ann Rheum Dis* 2015;74(9):1706-13.
39. Chen HL, Shen LJ, Hsu PN, et al. Cumulative Burden of Glucocorticoid-related Adverse Events in Patients with Systemic Lupus Erythematosus: Findings from a 12-year Longitudinal Study. *J Rheumatol* 2018;45(1):83-9.
40. Lim LSH, Pullenayegum E, Lim L, et al. From Childhood to Adulthood: The Trajectory of Damage in Patients With Juvenile-Onset Systemic Lupus Erythematosus. *Arthritis Care Res (Hoboken)* 2017;69(11):1627-35.
41. Yee CS, Su L, Toescu V, et al. Birmingham SLE cohort: outcomes of a large inception cohort followed for up to 21 years. *Rheumatology (Oxford)* 2015;54(5):836-43.

42. Al Sawah S, Zhang X, Zhu B, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus-the Hopkins Lupus Cohort. *Lupus Sci Med* 2015;2(1):e000066.
43. Ruiz-Arruza I, Barbosa C, Ugarte A, et al. Comparison of high versus low-medium prednisone doses for the treatment of systemic lupus erythematosus patients with high activity at diagnosis. *Autoimmun Rev* 2015;14(10):875-9.
44. Thamer M, Hernan MA, Zhang Y, et al. Prednisone, lupus activity, and permanent organ damage. *J Rheumatol* 2009;36(3):560-4.
45. Buttgerit F, da Silva JA, Boers M, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002;61(8):718-22.
46. Ruiz-Arruza I, Lozano J, Cabezas-Rodriguez I, et al. Restrictive Use of Oral Glucocorticoids in Systemic Lupus Erythematosus and Prevention of Damage Without Worsening Long-Term Disease Control: An Observational Study. *Arthritis Care Res (Hoboken)* 2018;70(4):582-591
47. Ruiz-Irastorza G, Ugarte A, Saint-Pastou Terrier C, et al. Repeated pulses of methyl-prednisolone with reduced doses of prednisone improve the outcome of class III, IV and V lupus nephritis: An observational comparative study of the Lupus-Cruces and lupus-Bordeaux cohorts. *Autoimmun Rev* 2017;16(8):826-32.
48. Singh JA, Hossain A, Kotb A, et al. Risk of serious infections with immunosuppressive drugs and glucocorticoids for lupus nephritis: a systematic review and network meta-analysis. *BMC Med* 2016;14(1):137.
49. Pego-Reigosa JM, Cobo-Ibanez T, Calvo-Alen J, et al. Efficacy and safety of nonbiologic immunosuppressants in the treatment of nonrenal systemic lupus erythematosus: a systematic review. *Arthritis Care Res (Hoboken)* 2013;65(11):1775-85.
50. Sakthiswary R, Suresh E. Methotrexate in systemic lupus erythematosus: a systematic review of its efficacy. *Lupus* 2014;23(3):225-35.
51. Mok CC. Mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus: a systematic review. *Scand J Rheumatol* 2007;36(5):329-37.

52. Tselios K, Gladman DD, Su J, et al. Mycophenolate Mofetil in Nonrenal Manifestations of Systemic Lupus Erythematosus: An Observational Cohort Study. *J Rheumatol* 2016;43(3):552-8.
53. Touma Z, Gladman DD, Urowitz MB, et al. Mycophenolate mofetil for induction treatment of lupus nephritis: a systematic review and metaanalysis. *J Rheumatol* 2011;38(1):69-78.
54. Ordi-Ros J, Saez-Comet L, Perez-Conesa M, et al. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. *Ann Rheum Dis* 2017;76(9):1575-82.
55. Knight JH, Howards PP, Spencer JB, et al. Characteristics related to early secondary amenorrhoea and pregnancy among women diagnosed with systemic lupus erythematosus: an analysis using the GOAL study. *Lupus Sci Med* 2016;3(1):e000139.
56. Mok CC, Chan PT, To CH. Anti-mullerian hormone and ovarian reserve in systemic lupus erythematosus. *Arthritis Rheum* 2013;65(1):206-10.
57. Tamirou F, Husson SN, Gruson D, et al. Brief Report: The Euro-Lupus Low-Dose Intravenous Cyclophosphamide Regimen Does Not Impact the Ovarian Reserve, as Measured by Serum Levels of Anti-Mullerian Hormone. *Arthritis Rheumatol* 2017;69(6):1267-71.
58. Blumenfeld Z, Mischari O, Schultz N, et al. Gonadotropin releasing hormone agonists may minimize cyclophosphamide associated gonadotoxicity in SLE and autoimmune diseases. *Semin Arthritis Rheum* 2011;41(3):346-52.
59. Marder W, McCune WJ, Wang L, et al. Adjunctive GnRH-a treatment attenuates depletion of ovarian reserve associated with cyclophosphamide therapy in premenopausal SLE patients. *Gynecol Endocrinol* 2012;28(8):624-7.
60. Bernatsky S, Ramsey-Goldman R, Joseph L, et al. Lymphoma risk in systemic lupus: effects of disease activity versus treatment. *Ann Rheum Dis* 2014;73(1):138-42.
61. Hsu CY, Lin MS, Su YJ, et al. Cumulative immunosuppressant exposure is associated with diversified cancer risk among 14 832 patients with systemic lupus erythematosus: a nested case-control study. *Rheumatology (Oxford)* 2017;56(4):620-8.

62. Cobo-Ibanez T, Loza-Santamaria E, Pego-Reigosa JM, et al. Efficacy and safety of rituximab in the treatment of non-renal systemic lupus erythematosus: a systematic review. *Semin Arthritis Rheum* 2014;44(2):175-85.
63. Merrill JT, Neuwelt CM, Wallace DJ, et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. *Arthritis Rheum* 2010;62(1):222-33.
64. Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: The lupus nephritis assessment with rituximab (LUNAR) study. *Arthritis Rheum* 2012;64(4):1215-26
65. Furie R, Petri M, Zamani O, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011;63(12):3918-30.
66. Navarra SV, Guzman RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet* 2011;377(9767):721-31.
67. Iaccarino L, Andreoli L, Bocci EB, et al. Clinical predictors of response and discontinuation of belimumab in patients with systemic lupus erythematosus in real life setting. Results of a large, multicentric, nationwide study. *J Autoimmun* 2018;86:1-8.
68. Manzi S, Sanchez-Guerrero J, Merrill JT, et al. Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. *Ann Rheum Dis* 2012;71(11):1833-8.
69. van Vollenhoven RF, Petri MA, Cervera R, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. *Ann Rheum Dis* 2012;71(8):1343-9.
70. Diaz-Lagares C, Croca S, Sangle S, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: Pooled data from European cohorts. *Autoimmun Rev* 2012;11(5):357-64
71. Duxbury B, Combescure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. *Lupus* 2013;22(14):1489-503.

72. Iaccarino L, Bartoloni E, Carli L, et al. Efficacy and safety of off-label use of rituximab in refractory lupus: data from the Italian Multicentre Registry. *Clin Exp Rheumatol* 2015;33(4):449-56.
73. Ramos-Casals M, Soto MJ, Cuadrado MJ, et al. Rituximab in systemic lupus erythematosus: A systematic review of off-label use in 188 cases. *Lupus* 2009;18(9):767-76.
74. Olfat M, Silverman ED, Levy DM. Rituximab therapy has a rapid and durable response for refractory cytopenia in childhood-onset systemic lupus erythematosus. *Lupus* 2015;24(9):966-72.
75. Terrier B, Amoura Z, Ravaud P, et al. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. *Arthritis Rheum* 2010;62(8):2458-66.
76. Chugh S, Darvish-Kazem S, Lim W, et al. Rituximab plus standard of care for treatment of primary immune thrombocytopenia: a systematic review and meta-analysis. *Lancet Haematol* 2015;2(2):e75-81.
77. Boletis JN, Marinaki S, Skalioti C, et al. Rituximab and mycophenolate mofetil for relapsing proliferative lupus nephritis: a long-term prospective study. *Nephrol Dial Transplant* 2009;24(7):2157-60.
78. Gomez Mendez LM, Cascino MD, Garg J, et al. Peripheral Blood B Cell Depletion after Rituximab and Complete Response in Lupus Nephritis. *Clin J Am Soc Nephrol* 2018;13(10):1502-9.
79. Kuhn A, Aberer E, Bata-Csorgo Z, et al. S2k guideline for treatment of cutaneous lupus erythematosus - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *J Eur Acad Dermatol Venereol* 2017;31(3):389-404.
80. Jewell ML, McCauliffe DP. Patients with cutaneous lupus erythematosus who smoke are less responsive to antimalarial treatment. *J Am Acad Dermatol* 2000;42(6):983-7.
81. Kuhn A, Gensch K, Haust M, et al. Photoprotective effects of a broad-spectrum sunscreen in ultraviolet-induced cutaneous lupus erythematosus: a randomized, vehicle-controlled, double-blind study. *J Am Acad Dermatol* 2011;64(1):37-48.
82. Kreuter A, Gambichler T, Breuckmann F, et al. Pimecrolimus 1% cream for cutaneous lupus erythematosus. *J Am Acad Dermatol* 2004;51(3):407-10.
83. Kuhn A, Gensch K, Haust M, et al. Efficacy of tacrolimus 0.1% ointment in cutaneous lupus erythematosus: a multicenter, randomized, double-blind, vehicle-controlled trial. *J Am Acad Dermatol* 2011;65(1):54-64,e1-2.

84. Costedoat-Chalumeau N, Dunogue B, Leroux G, et al. A Critical Review of the Effects of Hydroxychloroquine and Chloroquine on the Eye. *Clin Rev Allergy Immunol* 2015;49(3):317-26.
85. Chasset F, Arnaud L, Jachiet M, et al. Changing antimalarial agents after inefficacy or intolerance in patients with cutaneous lupus erythematosus: A multicenter observational study. *J Am Acad Dermatol* 2018;78(1):107-14 e1.
86. Chasset F, Bouaziz JD, Costedoat-Chalumeau N, et al. Efficacy and comparison of antimalarials in cutaneous lupus erythematosus subtypes: a systematic review and meta-analysis. *Br J Dermatol* 2017;177(1):188-96.
87. Cavazzana I, Sala R, Bazzani C, et al. Treatment of lupus skin involvement with quinacrine and hydroxychloroquine. *Lupus* 2009;18(8):735-9.
88. Fruchter R, Kurtzman DJB, Patel M, et al. Characteristics and Alternative Treatment Outcomes of Antimalarial-Refractory Cutaneous Lupus Erythematosus. *JAMA Dermatol* 2017;153(9):937-9.
89. Wenzel J, Brahler S, Bauer R, et al. Efficacy and safety of methotrexate in recalcitrant cutaneous lupus erythematosus: results of a retrospective study in 43 patients. *Br J Dermatol* 2005;153(1):157-62.
90. Gammon B, Hansen C, Costner MI. Efficacy of mycophenolate mofetil in antimalarial-resistant cutaneous lupus erythematosus. *J Am Acad Dermatol* 2011;65(4):717-21.
91. Kreuter A, Tomi NS, Weiner SM, et al. Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *Br J Dermatol* 2007;156(6):1321-7.
92. Md Yusof MY, Shaw D, El-Sherbiny YM, et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. *Ann Rheum Dis* 2017;76(11):1829-36.
93. Vital EM, Wittmann M, Edward S, et al. Brief report: responses to rituximab suggest B cell-independent inflammation in cutaneous systemic lupus erythematosus. *Arthritis Rheumatol* 2015;67(6):1586-91.
94. Fernandez-Nebro A, de la Fuente JL, Carreno L, et al. Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. *Lupus* 2012;21(10):1063-76.

95. Chasset F, Tounsi T, Cesbron E, et al. Efficacy and tolerance profile of thalidomide in cutaneous lupus erythematosus: A systematic review and meta-analysis. *J Am Acad Dermatol* 2018;78(2):342-50 e4.
96. Cortes-Hernandez J, Torres-Salido M, Castro-Marrero J, et al. Thalidomide in the treatment of refractory cutaneous lupus erythematosus: prognostic factors of clinical outcome. *Br J Dermatol* 2012;166(3):616-23.
97. Bortoluzzi A, Scire CA, Bombardieri S, et al. Development and validation of a new algorithm for attribution of neuropsychiatric events in systemic lupus erythematosus. *Rheumatology (Oxford)* 2015;54(5):891-8
98. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42(4):599-608.
99. Bortoluzzi A, Fanouriakis A, Appenzeller S, et al. Validity of the Italian algorithm for the attribution of neuropsychiatric events in systemic lupus erythematosus: a retrospective multicentre international diagnostic cohort study. *BMJ Open* 2017;7(5):e015546.
100. Magro-Checa C, Zirkzee EJ, Beart-van de Voorde LJJ, et al. Value of multidisciplinary reassessment in attribution of neuropsychiatric events to systemic lupus erythematosus: prospective data from the Leiden NPSLE cohort. *Rheumatology (Oxford)* 2017;56(10):1676-83.
101. Bertias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. *Nat Rev Rheumatol* 2010;6(6):358-67.
102. Bortoluzzi A, Padovan M, Farina I, et al. Therapeutic strategies in severe neuropsychiatric systemic lupus erythematosus: experience from a tertiary referral centre. *Reumatismo* 2012;64(6):350-9.
103. Dale RC, Brilot F, Duffy LV, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* 2014;83(2):142-50.
104. Fanouriakis A, Pamfil C, Sidiropoulos P, et al. Cyclophosphamide in combination with glucocorticoids for severe neuropsychiatric systemic lupus erythematosus: a retrospective, observational two-centre study. *Lupus* 2016;25(6):627-36.
105. Gupta N, Ganpati A, Mandal S, et al. Mycophenolate mofetil and deflazacort combination in neuropsychiatric lupus: a decade of experience from a tertiary care teaching hospital in southern India. *Clin Rheumatol* 2017;36(10):2273-9.

106. Narvaez J, Rios-Rodriguez V, de la Fuente D, et al. Rituximab therapy in refractory neuropsychiatric lupus: current clinical evidence. *Semin Arthritis Rheum* 2011;41(3):364-72.
107. Reiner P, Galanaud D, Leroux G, et al. Long-term outcome of 32 patients with chorea and systemic lupus erythematosus or antiphospholipid antibodies. *Mov Disord* 2011;26(13):2422-7.
108. Pamfil C, Fanouriakis A, Damian L, et al. EULAR recommendations for neuropsychiatric systemic lupus erythematosus vs usual care: results from two European centres. *Rheumatology (Oxford)* 2015;54(7):1270-8
109. Jung JH, Soh MS, Ahn YH, et al. Thrombocytopenia in Systemic Lupus Erythematosus: Clinical Manifestations, Treatment, and Prognosis in 230 Patients. *Medicine (Baltimore)* 2016;95(6):e2818.
110. Serris A, Amoura Z, Canoui-Poitrine F, et al. Efficacy and safety of rituximab for systemic lupus erythematosus-associated immune cytopenias: A multicenter retrospective cohort study of 71 adults. *Am J Hematol* 2018;93(3):424-9.
111. Chaturvedi S, Arnold DM, McCrae KR. Splenectomy for immune thrombocytopenia: down but not out. *Blood* 2018;131(11):1172-82.
112. You YN, Tefferi A, Nagorney DM. Outcome of splenectomy for thrombocytopenia associated with systemic lupus erythematosus. *Ann Surg* 2004;240(2):286-92.
113. Artim-Esen B, Cene E, Sahinkaya Y, et al. Cluster analysis of autoantibodies in 852 patients with systemic lupus erythematosus from a single center. *J Rheumatol* 2014;41(7):1304-10.
114. Duarte-Garcia A, Barr E, Magder LS, et al. Predictors of incident proteinuria among patients with SLE. *Lupus Sci Med* 2017;4(1):e000200.
115. Tang X, Huang Y, Deng W, et al. Clinical and serologic correlations and autoantibody clusters in systemic lupus erythematosus: a retrospective review of 917 patients in South China. *Medicine (Baltimore)* 2010;89(1):62-7.
116. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002;46(8):2121-31.

117. Houssiau FA, Vasconcelos C, D'Cruz D, et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. *Ann Rheum Dis* 2010;69(1):61-4.
118. Rijnink EC, Teng YKO, Wilhelmus S, et al. Clinical and Histopathologic Characteristics Associated with Renal Outcomes in Lupus Nephritis. *Clin J Am Soc Nephrol* 2017;12(5):734-43.
119. Walsh M, Solomons N, Lisk L, et al. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis with poor kidney function: a subgroup analysis of the Aspreva Lupus Management Study. *Am J Kidney Dis* 2013;61(5):710-5.
120. Houssiau FA, Vasconcelos C, D'Cruz D, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum* 2004;50(12):3934-40.
121. Dooley MA, Jayne D, Ginzler EM, et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011;365(20):1886-95.
122. Houssiau FA, D'Cruz D, Sangle S, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. *Ann Rheum Dis* 2010;69(12):2083-9.
123. Chen W, Tang X, Liu Q, et al. Short-term outcomes of induction therapy with tacrolimus versus cyclophosphamide for active lupus nephritis: A multicenter randomized clinical trial. *Am J Kidney Dis* 2011;57(2):235-44.
124. Lee YH, Lee HS, Choi SJ, et al. Efficacy and safety of tacrolimus therapy for lupus nephritis: a systematic review of clinical trials. *Lupus* 2011;20(6):636-40.
125. Miyasaka N, Kawai S, Hashimoto H. Efficacy and safety of tacrolimus for lupus nephritis: a placebo-controlled double-blind multicenter study. *Mod Rheumatol* 2009;19(6):606-15.
126. Bao H, Liu ZH, Xie HL, et al. Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 2008;19(10):2001-10.
127. Liu Z, Zhang H, Xing C, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med* 2015;162(1):18-26.

128. Szeto CC, Kwan BC, Lai FM, et al. Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. *Rheumatology (Oxford)* 2008;47(11):1678-81.
129. Uchino A, Tsukamoto H, Nakashima H, et al. Tacrolimus is effective for lupus nephritis patients with persistent proteinuria. *Clin Exp Rheumatol* 2010;28(1):6-12.
130. Ikeuchi H, Hiromura K, Takahashi S, et al. Efficacy and safety of multi-target therapy using a combination of tacrolimus, mycophenolate mofetil and a steroid in patients with active lupus nephritis. *Mod Rheumatol* 2014;24(4):618-25.
131. Kasitanon N, Boripatkosol P, Louthrenoo W. Response to combination of mycophenolate mofetil, cyclosporin A and corticosteroid treatment in lupus nephritis patients with persistent proteinuria. *Int J Rheum Dis* 2018;21(1):200-7.
132. Mok CC, To CH, Yu KL, et al. Combined low-dose mycophenolate mofetil and tacrolimus for lupus nephritis with suboptimal response to standard therapy: a 12-month prospective study. *Lupus* 2013;22(11):1135-41.
133. Conti F, Ceccarelli F, Perricone C, et al. The chronic damage in systemic lupus erythematosus is driven by flares, glucocorticoids and antiphospholipid antibodies: results from a monocentric cohort. *Lupus* 2016;25(7):719-26.
134. Taraborelli M, Leuenberger L, Lazzaroni MG, et al. The contribution of antiphospholipid antibodies to organ damage in systemic lupus erythematosus. *Lupus* 2016;25(12):1365-8.
135. Arnaud L, Mathian A, Ruffatti A, et al. Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: an international and collaborative meta-analysis. *Autoimmun Rev* 2014;13(3):281-91.
136. Group ASC, Bowman L, Mafham M, et al. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med* 2018;379(16):1529-39.
137. Ridker PM. Should Aspirin Be Used for Primary Prevention in the Post-Statin Era? *N Engl J Med* 2018;379(16):1572-4.
138. Pengo V, Ruffatti A, Legnani C, et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *J Thromb Haemost* 2010;8(2):237-42.

139. Pengo V, Denas G, Zoppellaro G, et al. Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood* 2018;132(13):1365-1371
140. Chen D, Xie J, Chen H, et al. Infection in Southern Chinese Patients with Systemic Lupus Erythematosus: Spectrum, Drug Resistance, Outcomes, and Risk Factors. *J Rheumatol* 2016;43(9):1650-6.
141. Rúa-Figueroa I, Lopez-Longo J, Galindo-Izquierdo M, et al. Incidence, associated factors and clinical impact of severe infections in a large, multicentric cohort of patients with systemic lupus erythematosus. *Semin Arthritis Rheum* 2017;47(1):38-45.
142. Costa-Reis P, Nativ S, Isgro J, et al. Major infections in a cohort of 120 patients with juvenile-onset systemic lupus erythematosus. *Clin Immunol* 2013;149(3):442-9.
143. Hiraki LT, Feldman CH, Marty FM, et al. Serious Infection Rates Among Children With Systemic Lupus Erythematosus Enrolled in Medicaid. *Arthritis Care Res (Hoboken)* 2017;69(11):1620-6.
144. Elkayam O, et al Update of EULAR recommendations for vaccination of patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2018;(77):41.
145. van Assen S, Agmon-Levin N, Elkayam O, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2011;70(3):414-22.
146. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315(8):762-74.
147. Ballocca F, D'Ascenzo F, Moretti C, et al. Predictors of cardiovascular events in patients with systemic lupus erythematosus (SLE): a systematic review and meta-analysis. *Eur J Prev Cardiol* 2015;22(11):1435-41.
148. Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. *Am J Epidemiol* 2012;176(8):708-19.
149. Wu GC, Liu HR, Leng RX, et al. Subclinical atherosclerosis in patients with systemic lupus erythematosus: A systemic review and meta-analysis. *Autoimmun Rev* 2016;15(1):22-37.
150. Gustafsson JT, Svenungsson E. Definitions of and contributions to cardiovascular disease in systemic lupus erythematosus. *Autoimmunity* 2014;47(2):67-76.

151. Fasano S, Pierro L, Pantano I, et al. Longterm Hydroxychloroquine Therapy and Low-dose Aspirin May Have an Additive Effectiveness in the Primary Prevention of Cardiovascular Events in Patients with Systemic Lupus Erythematosus. *J Rheumatol* 2017;44(7):1032-8.
152. Iudici M, Fasano S, Gabriele Falcone L, et al. Low-dose aspirin as primary prophylaxis for cardiovascular events in systemic lupus erythematosus: a long-term retrospective cohort study. *Rheumatology (Oxford)* 2016;55(9):1623-30.
153. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018;392(10152):1036-46.
154. Petri MA, Kiani AN, Post W, et al. Lupus Atherosclerosis Prevention Study (LAPS). *Ann Rheum Dis* 2011;70(5):760-5.
155. Schanberg LE, Sandborg C, Barnhart HX, et al. Use of atorvastatin in systemic lupus erythematosus in children and adolescents. *Arthritis Rheum* 2012;64(1):285-96.
156. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J* 2016;37(29):2315-81.
157. Moroni G, Raffiotta F, Ponticelli C. Remission and withdrawal of therapy in lupus nephritis. *J Nephrol* 2016;29(4):559-65.
158. Piñeiro GJ, Arrizabalaga P, Solé M, et al. Repeated renal biopsy – A predictive tool to assess the probability of renal flare in lupus nephritis. *Am J Nephrol* 2016; 44(6):439-46.
159. De Rosa M, Azzato F, Toblli JE, et al. A prospective observational cohort study highlights kidney biopsy findings of lupus nephritis patients in remission who flare following withdrawal of maintenance therapy. *Kidney Int* 2018;94(4):788-94.