

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

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ABSTRACT

Our objective was to update the EULAR recommendations for the management of systemic lupus erythematosus (SLE), based on emerging new evidence. We performed a systematic literature review (01/2007–12/2017), followed by modified Delphi method, to form questions, elicit expert opinions and reach consensus. Treatment in SLE aims at remission or low disease activity and prevention of flares. Hydroxychloroquine is recommended in all patients with lupus, at a dose not exceeding 5 mg/kg real body weight. During chronic maintenance treatment, glucocorticoids (GC) should be minimised to less than 7.5 mg/day (prednisone equivalent) and, when possible, withdrawn.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 GC. In persistently active or flaring extrarenal disease, add-on belimumab should be considered; rituximab (RTX) may be considered in organ-threatening, refractory disease. Updated specific recommendations are also provided for cutaneous, neuropsychiatric, haematological and renal disease. Patients with SLE should be assessed for their antiphospholipid antibody status, infectious and cardiovascular diseases risk profile and preventative strategies be tailored accordingly. The updated recommendations provide physicians and patients with updated consensus guidance on the management of SLE, combining evidence-base and expert-opinion.

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 biological therapy for SLE. These advances called for an update of

the EULAR recommendations for lupus, capitalising 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 (online 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: (1) treatment of skin disease, where an unrestricted date search was performed and (2) renal disease, where 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 online 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 online supplementary table 4). After rounds of discussions, the committee reached a consensus of 33 final statements, grouped in four broad categories (Goals of Treatment, Treatment of SLE, Specific manifestations, Comorbidities—table 1). Each Task Force member rated their agreement with each statement.



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Recommendation

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

Recommendation/Statement	Level of agreement, mean (SD)
Overarching principles	
▶ SLE is a multisystem disease—occasionally limited to one or few organs—diagnosed on clinical grounds in the presence of characteristic serological abnormalities.	
▶ SLE care is multidisciplinary, based on a shared patient-physician decision, and should consider individual, medical and societal costs.	
▶ Treatment of organ-threatening/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.	
▶ Treatment goals include long-term patient survival, prevention of organ damage and optimisation of health-related quality of life.	
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 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, ophthalmological screening (by visual fields examination and/or spectral domain-optical coherence tomography) should be performed at baseline, after 5 years, and yearly thereafter (2b/B).	9.75 (0.70)
2.2 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 minimised 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 <i>methotrexate</i> , (1b/B) <i>azathioprine</i> (2b/C) or <i>mycophenolate</i> (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 <i>Cyclophosphamide</i> can be used for severe organ-threatening 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 <i>belimumab</i> 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, <i>rituximab</i> 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 <i>topical agents</i> (GC, calcineurin inhibitors) (2b/B), <i>antimalarials</i> (HCQ, quinacrine) (1a/A) and/or <i>systemic GC</i> (4/C).	10.0 (0)
3.1.2 In non-responsive cases or cases requiring high-dose GC, <i>methotrexate</i> (3a/B), <i>retinoids</i> (4/C), <i>dapsone</i> (4/C) or <i>mycophenolate</i> (4/C) can be added.	9.85 (0.48)
3.2 Neuropsychiatric disease	
3.2.1 <i>Attribution</i> 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 aPL) and exclusion of confounding factors (2b/C).	9.65 (0.85)
3.2.2 <i>Treatment</i> 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 Haematological disease	
3.3.1 <i>Acute treatment</i> 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 <i>mycophenolate</i> (2b/C), <i>azathioprine</i> (2b/C) or <i>cyclosporine</i> (4/C) can be used.	9.75 (0.62)
3.3.3 Refractory cases can be treated with <i>rituximab</i> (3a/C) or <i>cyclophosphamide</i> (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 <i>Mycophenolate</i> (1a/A) or <i>low-dose intravenous cyclophosphamide</i> (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, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis), similar regimens may be considered but high-dose intravenous cyclophosphamide can also be used (1b/A).	9.45 (0.80)
3.4.4 For maintenance therapy, <i>mycophenolate</i> (1a/A) or <i>azathioprine</i> (1a/A) should be used.	9.75 (0.62)

Continued

Table 1 Continued

Recommendation/Statement	Level of agreement, mean (SD)
3.4.5 In cases with stable/improved renal function but <i>incomplete renal response</i> (persistent proteinuria >0.8–1 g/24 hours after at least 1 year of immunosuppressive treatment), <i>repeat biopsy</i> 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 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.	9.50 (0.81)
4 Comorbidities	
4.1 Antiphospholipid syndrome	
4.1.1 All patients with SLE should be screened at diagnosis for aPL (1a/A).	10.0 (0)
4.1.2 Patients with SLE 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 antiphospholipid syndrome (1b/B).	10.0 (0)
4.2 Infectious diseases	
4.2.1 Patients with SLE should be assessed for <i>general and disease-related risk factors</i> for infections, such as advanced age/frailty (–/D), diabetes mellitus (–/D), renal involvement (2b/B), immunosuppressive/biological therapy (1b-2b/B-C) and use of GC (1a/A).	9.85 (0.65)
4.2.2 General preventative measures (including immunisations) 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 <i>traditional (1b/B-C) and disease-related risk factors</i> 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, patients with SLE may be candidates for preventative strategies as in the general population, including <i>low-dose aspirin (2b/D) and/or lipid-lowering agents (2b/D)</i> .	9.85 (0.48)

aPL, antiphospholipid antibodies; GC, glucocorticoids; GFR, glomerular filtration rate; HCQ, hydroxychloroquine; SLE, systemic lupus erythematosus.

RESULTS AND DISCUSSION

Overarching principles

SLE represents a challenge for the treating physician in terms of diagnosis and treatment. Its protean manifestations, often multi-system but occasionally limited to a few or single organ, have led some physicians to focus exclusively on evidence of serological autoimmunity (antinuclear 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 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/24 hours 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 g/day) 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 generalised disease activity and serological 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

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 pre-existing 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

Recommendation

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.

Glucocorticoids

GC can provide rapid symptom relief, but the medium to long-term aim should be to minimise 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: (1) use of pulses of intravenous methylprednisolone (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 (2) early initiation of IS agents, to facilitate tapering and eventual discontinuation of oral GC (*see below*). High-dose intravenous MP (usually 250–1000 mg/day for 3 days) is often used in acute, organ-threatening disease (eg, renal, neuropsychiatric) after excluding infections.⁴⁸

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 randomised, 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 with 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 analogues attenuates the depletion of ovarian reserve associated with CYC therapy and is recommended in premenopausal patients with SLE.^{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}

Biological 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 (ie, maximum 7.5 mg/day). Patients with persistent disease may benefit from belimumab; more likely to respond are patients with high disease activity (eg, SLEDAI >10), prednisone dose >7.5 mg/day and serological activity (low C3/C4, high anti-dsDNA titres), with cutaneous, musculoskeletal and serological manifestations responding the most.^{67–69}

Due to the negative results of randomised controlled trials (RCTs), RTX is currently only used off-label, in patients with severe renal or extrarenal (mainly haematological 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 haemolytic anaemia, where RTX has demonstrated efficacy both in lupus and in patients with isolated immune thrombocytopenia (ITP).^{74–76} In LN, RTX is typically considered following failure of first-line therapies (CYC, MMF) or in relapsing disease.^{70 77} More recently, a *posthoc* 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 summarises the various drugs used in the treatment of SLE, according to disease severity stratification. Online supplementary table 5 outlines the recommended doses of the drugs mentioned in the manuscript.

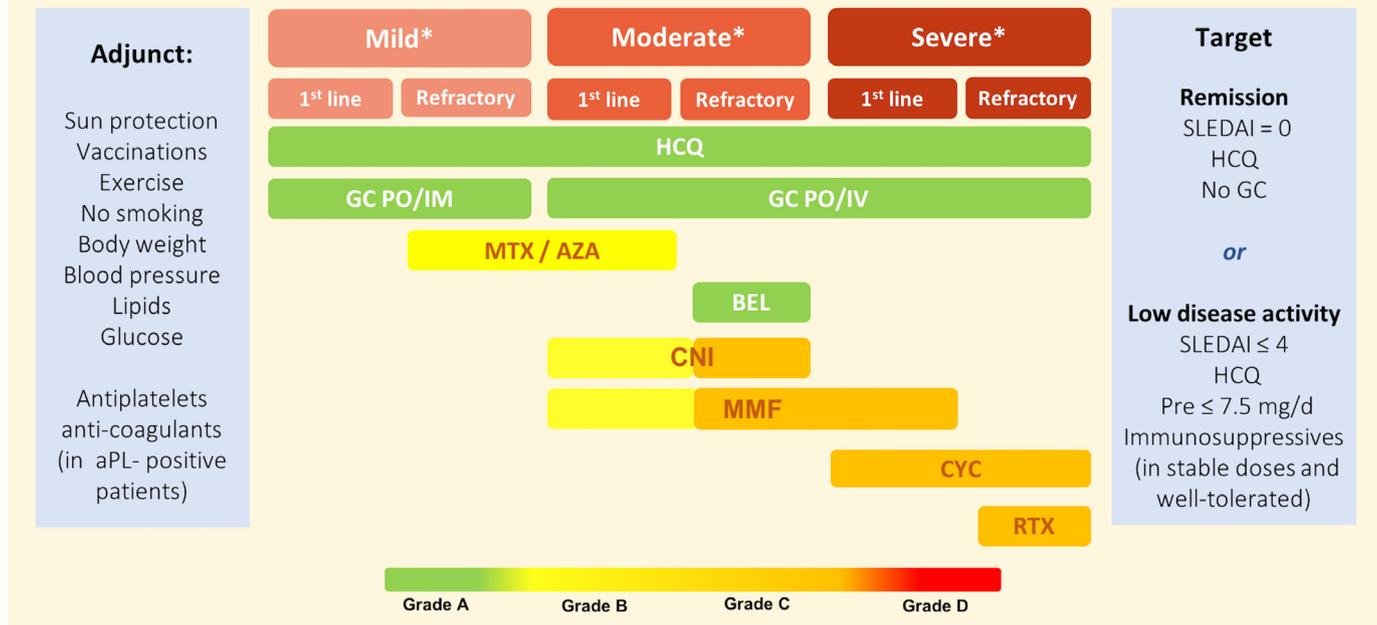
Specific manifestations

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 CNIs) 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} Although 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 on drug discontinuation, it should be considered only as a ‘rescue’ therapy in patients who have failed

Treatment of non-renal Systemic Lupus Erythematosus



Mild: constitutional symptoms/ mild arthritis/ rash ≤9% BSA/PLTs 50-100 x 10⁹/mm³; SLEDAI≤6; BILAG C or ≤1 BILAG B manifestation
Moderate: RA-like arthritis/ rash 9-18% BSA/cutaneous vasculitis ≤18% BSA; PLTs 20-50x10³/mm³/serositis; SLEDAI 7-12; ≥2 BILAG B manifestations
Severe: major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopenia with platelets <20x10³/mm³; TTP-like disease or acute hemophagocytic syndrome; SLEDAI>12; ≥1 BILAG A manifestations

Figure 1 Treatment of non-renal SLE—recommended drugs with respective grading of recommendation. aPL, antiphospholipid antibodies; AZA, azathioprine; BEL, belimumab; BILAG: British Isles Lupus Assessment Group disease activity index; CNIs, calcineurin inhibitors; CYC, cyclophosphamide; GC, glucocorticoids; HCQ, hydroxychloroquine; IM, intramuscular; MMF, mycophenolate mofetil; MTX, methotrexate; Pre, prednisone; PO, per os; RTX, rituximab; PLTs: Platelets; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

multiple previous agents. A treatment algorithm for the various subtypes of CLE 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

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 (*'favouring'*) factors (type and timing of manifestation, presence of generalised, non-neurological disease activity, abnormal neuroimaging and cerebrospinal fluid analysis, positive antiphospholipid antibodies [aPL]),⁹⁷ as well as confounding factors favouring 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 pathophysiological mechanism is presumed to be inflammatory or embolic/thrombotic/ischaemic.^{2, 101} GC and/or IS agents should be considered in the former, while anticoagulant/anti-thrombotic treatment is favoured when aPL antibodies are present.¹⁰²⁻¹⁰⁷ Distinction between the two pathophysiological 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. Patients with SLE 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 IS therapy. Targeted symptomatic therapy is indicated according to the type of manifestation (eg, antipsychotics for psychosis, anxiolytics for anxiety disorder and so on).

Haematological disease

Haematological manifestations frequently necessitating anti-inflammatory/IS treatment in patients with SLE include thrombocytopenia and autoimmune haemolytic anaemia (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 intravenous MP (1-3 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 characterised by relapses during GC tapering.¹⁰⁹ In patients with no response to GC (ie, 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 haemolytic anaemia (AIHA) is far less common than thrombocytopenia in SLE; its treatment follows the same principles regarding use of GC, IS drugs and RTX. Autoimmune leucopaenia is common in SLE but rarely needs treatment; careful work-up is recommended to exclude other causes of leucopaenia (especially drug-induced).

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 (eg, 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, online supplementary table 5) 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 (online supplementary table 5) in severe forms of LN associated with increased risk of progression into end-stage renal disease (reduced glomerular filtration rate, histological presence of fibrous crescents or fibrinoid necrosis, or tubular atrophy/interstitial fibrosis).^{118 119} An early significant drop in UPr (to ≤ 1 g/day at 6 months or ≤ 0.8 g/day at 12 months) is a predictor of favourable 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 CNIs to treat proliferative LN, either alone or in the form of a ‘multi-target 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

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 patients with lupus with any aPL antibodies or only to those carrying a high risk aPL profile (ie, triple aPL positivity, lupus anticoagulant or high titres of anticardiolipin antibodies).¹³⁸ Patients with SLE 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 patients with SLE-APS, 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 randomised, 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 normalised ratio on warfarin, after balancing possible risks.

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 leucopaenia and presence of renal involvement (\pm hypogammaglobulinaemia 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. Patients with lupus should receive vaccinations according to the EULAR recommendations for vaccination of patients with autoimmune rheumatic diseases.^{144 145} Immunisation 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 mm Hg, 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

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 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 as 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 **box 1**. 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

Box 1 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 calcineurin inhibitor-containing treatment regimens in lupus nephritis (LN) in different racial/ethnic groups and at longer time points.
- Usefulness of measurements of drug blood levels (hydroxychloroquine [HCQ], mycophenolate mofetil and so on).
- Efficacy of quinacrine as immunomodulator in patients with HCQ-induced retinal toxicity.
- Comparative trials of conventional immunosuppressive drugs with global and organ-specific result reporting.
- Randomised trials testing lower cumulative dose glucocorticoid regimens versus conventional regimens.
- Optimal treatment regimen of rituximab: 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 histological response to therapy.

Pathophysiology and Biomarkers

- Susceptibility to develop systemic lupus erythematosus (SLE).
- Involvement of particular organ systems over others, multisystem versus organ-dominant disease.
- Response to specific therapeutic agents over others (pharmacogenetics, transcriptomics and so on).

Clinical trial design and new drug development

- Optimisation of clinical trial design and study endpoints to maximise 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.

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}

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REFERENCES

- ¹ Bertias G, Ioannidis JPA, 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;67:195–205.

- 2 Bertsias GK, Ioannidis JPA, 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;69:2074–82.
- 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;71:1771–82.
- 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;76:476–85.
- 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;69:1269–74.
- 6 Boumpas DT, Bertsias GK, Fanouriakis A. 2008–2018: a decade of recommendations for systemic lupus erythematosus. *Ann Rheum Dis* 2018;77:1547–8.
- 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;74:8–13.
- 8 Brouwers MC, Kho ME, Browman GP, *et al.* Agree II: advancing Guideline Development, reporting and evaluation in health care. *CMAJ* 2010;182:E839–42.
- 9 Ward MM. Hospital experience and mortality in patients with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:891–8.
- 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;76:554–61.
- 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;73:958–67.
- 12 Medina-Quifones 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* 2016;68:981–7.
- 13 Steiman AJ, Urowitz MB, Ibañez D, *et al.* Prolonged clinical remission in patients with systemic lupus erythematosus. *J Rheumatol* 2014;41:1808–16.
- 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;76:2071–4.
- 15 Urowitz MB, Felejar M, Bruce IN, *et al.* Prolonged remission in systemic lupus erythematosus. *J Rheumatol* 2005;32:1467–72.
- 16 Zen M, Iaccarino L, Gatto M, *et al.* Prolonged remission in Caucasian patients with SLE: prevalence and outcomes. *Ann Rheum Dis* 2015;74:2117–22.
- 17 Tsang A-Sjoe MWP, Bultink IEM, Heslinga M, *et al.* Both prolonged remission and lupus low disease activity state are associated with reduced damage accrual in systemic lupus erythematosus. *Rheumatology* 2017;56:121–8.
- 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;77:104–10.
- 19 Polachek A, Gladman DD, Su J, *et al.* Defining low disease activity in systemic lupus erythematosus. *Arthritis Care Res* 2017;69:997–1003.
- 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* 2018.
- 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;67:1305–13.
- 22 Touma Z, Urowitz MB, Ibañez D, *et al.* Time to recovery from proteinuria in patients with lupus nephritis receiving standard treatment. *J Rheumatol* 2014;41:688–97.
- 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.
- 24 Ruperto N, Hanrahan LM, Alarcón GS, *et al.* International consensus for a definition of disease flare in lupus. *Lupus* 2011;20:453–62.
- 25 Koutsonikoli A, Trachana M, Heidich A-B, *et al.* Dissecting the damage in northern Greek patients with childhood-onset systemic lupus erythematosus: a retrospective cohort study. *Rheumatol Int* 2015;35:1225–32.
- 26 Ugarte-Gil MF, Acevedo-Vásquez E, Alarcón 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* 2015;74:1019–23.
- 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;75:1615–21.
- 28 Kasitanon N, Intaniwet T, Wangkaew S, *et al.* The clinically quiescent phase in early-diagnosed SLE patients: inception cohort study. *Rheumatology* 2015;54:868–75.
- 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;65:2143–53.
- 30 Steiman AJ, Gladman DD, Ibañez D, *et al.* Outcomes in patients with systemic lupus erythematosus with and without a prolonged serologically active clinically quiescent period. *Arthritis Care Res* 2012;64:511–8.
- 31 Weiss JE, Sison CP, Ilowite NT, *et al.* Flares in pediatric systemic lupus erythematosus. *J Rheumatol* 2007;34:1341–4.
- 32 Ruiz-Iratorza 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;69:20–8.
- 33 Costedoat-Chalumeau N, Amoura Z, Hulot J-S, *et al.* Very low blood hydroxychloroquine concentration as an objective marker of poor adherence to treatment of systemic lupus erythematosus. *Ann Rheum Dis* 2007;66:821–4.
- 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;27:265–72.
- 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* 2016;68:1295–302.
- 36 Melles RB, Marmor MF. The risk of toxic retinopathy in patients on long-term hydroxychloroquine therapy. *JAMA Ophthalmol* 2014;132:1453–60.
- 37 Kim J-W, Kim YY, Lee H, *et al.* Risk of retinal toxicity in longterm users of hydroxychloroquine. *J Rheumatol* 2017;44:1674–9.
- 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;74:1706–13.
- 39 Chen H-L, Shen L-J, Hsu P-N, *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;45:83–9.
- 40 LSH L, 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* 2017;69:1627–35.
- 41 Yee C-S, Su L, Toescu V, *et al.* Birmingham SLE cohort: outcomes of a large inception cohort followed for up to 21 years. *Rheumatology* 2015;54:836–43.
- 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:e000066.
- 43 Ruiz-Arzuza 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;14:875–9.
- 44 Thamer MAE, Hernan MA, Zhang YI, *et al.* Prednisone, lupus activity, and permanent organ damage. *J Rheumatol* 2009;36:560–4.
- 45 Buttgeriet F, da Silva JAP, Boers M, *et al.* Standardised Nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Ann Rheum Dis* 2002;61:718–22.
- 46 Ruiz-Arzuza I, Lozano J, Cabezas-Rodríguez 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* 2018;70:582–91.
- 47 Ruiz-Iratorza G, Ugarte A, Saint-Pastou Terrier C, *et al.* Repeated pulses of methylprednisolone 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;16:826–32.
- 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.
- 49 Pego-Reigosa JM, Cobo-Ibáñez T, Calvo-Alén J, *et al.* Efficacy and safety of nonbiologic immunosuppressants in the treatment of nonrenal systemic lupus erythematosus: a systematic review. *Arthritis Care Res* 2013;65:1775–85.
- 50 Sakthiswary R, Suresh E. Methotrexate in systemic lupus erythematosus: a systematic review of its efficacy. *Lupus* 2014;23:225–35.
- 51 Mok CC. Mycophenolate mofetil for non-renal manifestations of systemic lupus erythematosus: a systematic review. *Scand J Rheumatol* 2007;36:329–37.
- 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;43:552–8.
- 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;38:69–78.
- 54 Ordi-Ros J, Sáez-Comet L, Pérez-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;76:1575–82.
- 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:e000139.
- 56 Mok CC, Chan PT, To CH. Anti-Müllerian hormone and ovarian reserve in systemic lupus erythematosus. *Arthritis Rheum* 2013;65:206–10.
- 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-müllerian hormone. *Arthritis Rheumatol* 2017;69:1267–71.
- 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;41:346–52.
- 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;28:624–7.
- 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;73:138–42.
- 61 Hsu CY, Lin MS, YJ S, *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* 2017;56:620–8.
- 62 Cobo-Ibáñez T, Loza-Santamaría 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;44:175–85.
- 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;62:222–33.
- 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 study. *Arthritis Rheum* 2012;64:1215–26.
- 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;63:3918–30.
- 66 Navarra SV, Guzmán RM, Gallacher AE, *et al.* Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *The Lancet* 2011;377:721–31.
- 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, Sánchez-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;71:1833–8.
- 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;71:1343–9.
- 70 Díaz-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;11:357–64.
- 71 Duxbury B, Combesure C, Chizzolini C. Rituximab in systemic lupus erythematosus: an updated systematic review and meta-analysis. *Lupus* 2013;22:1489–503.
- 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;33:449–56.
- 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;18:767–76.
- 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;24:966–72.
- 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;62:2458–66.
- 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: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;24:2157–60.
- 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;13:1502–9.
- 79 Kuhn A, Aberer E, Bata-Csörgő 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 Venerology (EADV). *J Eur Acad Dermatol Venereol* 2017;31:389–404.
- 80 Jewell ML, McCauliffe DP. Patients with cutaneous lupus erythematosus who smoke are less responsive to antimalarial treatment. *J Am Acad Dermatol* 2000;42:983–7.
- 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;64:37–48.
- 82 Kreuter A, Gambichler T, Breuckmann F, *et al.* Pimecrolimus 1% cream for cutaneous lupus erythematosus. *J Am Acad Dermatol* 2004;51:407–10.
- 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;65:54–64.
- 84 Costedoat-Chalumeau N, Dunogué B, Leroux G, *et al.* A critical review of the effects of hydroxychloroquine and chloroquine on the eye. *Clin Rev Allergy Immunol* 2015;49:317–26.
- 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;78:107–14.
- 86 Chasset F, Bouaziz J-D, 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;177:188–96.
- 87 Cavazzana I, Sala R, Bazzani C, *et al.* Treatment of lupus skin involvement with quinine and hydroxychloroquine. *Lupus* 2009;18:735–9.
- 88 Fruchter R, Kurtzman DJB, Patel M, *et al.* Characteristics and alternative treatment outcomes of Antimalarial-Refractory cutaneous lupus erythematosus. *JAMA Dermatol* 2017;153:937–9.
- 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;153:157–62.
- 90 Gammon B, Hansen C, Costner MI. Efficacy of mycophenolate mofetil in antimalarial-resistant cutaneous lupus erythematosus. *J Am Acad Dermatol* 2011;65:717–21.
- 91 Kreuter A, Tomi NS, Weiner SM, *et al.* Mycophenolate sodium for subacute cutaneous lupus erythematosus resistant to standard therapy. *Br J Dermatol* 2007;156:1321–7.
- 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;76:1829–36.
- 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;67:1586–91.
- 94 Fernández-Nebro A, de la Fuente JLM, Carreño L, *et al.* Multicenter longitudinal study of B-lymphocyte depletion in refractory systemic lupus erythematosus: the LESIMAB study. *Lupus* 2012;21:1063–76.
- 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;78:342–50.
- 96 Cortés-Hernández 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;166:616–23.
- 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* 2015;54:891–8.
- 98 Acr ad hoc committee on neuropsychiatric lupus nomenclature. The American College of rheumatology Nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42:599–608.
- 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: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* 2017;56:1676–83.
- 101 Bertsias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. *Nat Rev Rheumatol* 2010;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;64:350–9.
- 103 Dale RC, Brilot F, Duffy LV, *et al.* Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. *Neurology* 2014;83:142–50.
- 104 Fanouriakis A, Pamfil C, Sidropoulos P, *et al.* Cyclophosphamide in combination with glucocorticoids for severe neuropsychiatric systemic lupus erythematosus: a retrospective, observational two-centre study. *Lupus* 2016;25:627–36.
- 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;36:2273–9.
- 106 Narváez J, Ríos-Rodríguez V, de la Fuente D, *et al.* Rituximab therapy in refractory neuropsychiatric lupus: current clinical evidence. *Semin Arthritis Rheum* 2011;41:364–72.
- 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;26:2422–7.
- 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* 2015;54:1270–8.
- 109 Jung J-H, Soh M-S, Ahn Y-H, *et al.* Thrombocytopenia in systemic lupus erythematosus: clinical manifestations, treatment, and prognosis in 230 patients. *Medicine* 2016;95: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;93:424–9.
- 111 Chaturvedi S, Arnold DM, McCrae KR. Splenectomy for immune thrombocytopenia: down but not out. *Blood* 2018;131:1172–82.
- 112 You YN, Tefferi A, Nagorney DM. Outcome of splenectomy for thrombocytopenia associated with systemic lupus erythematosus. *Ann Surg* 2004;240:286–92.
- 113 Artim-Esen B, Çene E, Şahinkaya Y, *et al.* Cluster analysis of autoantibodies in 852 patients with systemic lupus erythematosus from a single center. *J Rheumatol* 2014;41:1304–10.
- 114 Duarte-García A, Barr E, Magder LS, *et al.* Predictors of incident proteinuria among patients with SLE. *Lupus Sci Med* 2017;4: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* 2010;89:62–7.
- 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;46:2121–31.
- 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;69:61–4.
- 118 Rijink EC, Teng YKO, Wilhelmus S, *et al.* Clinical and histopathologic characteristics associated with renal outcomes in lupus nephritis. *Clin J Am Soc Nephrol* 2017;12:734–43.
- 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;61:710–5.
- 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;50:3934–40.
- 121 Dooley MA, Jayne D, Ginzler EM, *et al.* Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011;365:1886–95.
- 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;69:2083–9.
- 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;57:235–44.
- 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;20:636–40.
- 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;19:606–15.
- 126 Bao H, Liu Z-H, Xie H-L, *et al.* Successful treatment of class V+IV lupus nephritis with multitarget therapy. *J Am Soc Nephrol* 2008;19:2001–10.
- 127 Liu Z, Zhang H, Liu Z, *et al.* Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. *Ann Intern Med* 2015;162:18–26.
- 128 Szeto C-C, Kwan BC-H, Lai FM-M, *et al.* Tacrolimus for the treatment of systemic lupus erythematosus with pure class V nephritis. *Rheumatology* 2008;47:1678–81.
- 129 Uchino A, Tsukamoto H, Nakashima H, *et al.* Tacrolimus is effective for lupus nephritis patients with persistent proteinuria. *Clin Exp Rheumatol* 2010;28:6–12.
- 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;24:618–25.
- 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;21:200–7.
- 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;22:1135–41.
- 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;25:719–26.
- 134 Taraborelli M, Leuenberger L, Lazzaroni MG, *et al.* The contribution of antiphospholipid antibodies to organ damage in systemic lupus erythematosus. *Lupus* 2016;25:1365–8.
- 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;13:281–91.
- 136 Bowman L, Mafham M, Wallendszus K, *et al.* Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018;379:1529–39.
- 137 Ridker PM. Should aspirin be used for primary prevention in the Post-Statins era? *N Engl J Med* 2018;379:1572–4.
- 138 Pengo V, Ruffatti A, Legnani C, *et al.* Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. *J Thromb Haemost* 2010;8:237–42.
- 139 Pengo V, Denas G, Zoppellaro G, *et al.* Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome. *Blood* 2018;132:1365–71.
- 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;43:1650–6.
- 141 Rúa-Figueroa Íñigo, López-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;47:38–45.
- 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;149:442–9.
- 143 Hiraki LT, Feldman CH, Marty FM, *et al.* Serious infection rates among children with systemic lupus erythematosus enrolled in Medicaid. *Arthritis Care Res* 2017;69:1620–6.
- 144 Elkayam O *et al.* Update of EULAR recommendations for vaccination of patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2018;77.
- 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;70:414–22.
- 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;315:762–74.
- 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;22:1435–41.
- 148 Magder LS, Petri M. Incidence of and risk factors for adverse cardiovascular events among patients with systemic lupus erythematosus. *Am J Epidemiol* 2012;176:708–19.
- 149 Wu G-C, Liu H-R, Leng R-X, *et al.* Subclinical atherosclerosis in patients with systemic lupus erythematosus: a systemic review and meta-analysis. *Autoimmun Rev* 2016;15:22–37.
- 150 Gustafsson JT, Svenungsson E. Definitions of and contributions to cardiovascular disease in systemic lupus erythematosus. *Autoimmunity* 2014;47:67–76.
- 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;44:1032–8.
- 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* 2016;55:1623–30.
- 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;392:1036–46.
- 154 Petri MA, Kiani AN, Post W, *et al.* Lupus atherosclerosis prevention study (LAPS). *Ann Rheum Dis* 2011;70:760–5.
- 155 Schanberg LE, Sandborg C, Barnhart HX, *et al.* Use of atorvastatin in systemic lupus erythematosus in children and adolescents. *Arthritis Rheum* 2012;64:285–96.
- 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;37:2315–81.
- 157 Moroni G, Raffiotta F, Ponticelli C. Remission and withdrawal of therapy in lupus nephritis. *J Nephrol* 2016;29:559–65.
- 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;44:439–46.
- 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;94:788–94.