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

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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treatment, glucocorticoids should be minimized to less than 7.5 mg/day (prednisone equivalent) and, when possible, withdrawn.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 procedures[7] 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	
• SLE is a multisystem disease - occasionally limited to one or few organs - diagnosed on clinical grounds in the presence of characteristic serologic abnormalities.	
• SLE care is multidisciplinary, based on a shared patient-physician decision, and should consider individual, medical and societal costs.	
• 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.	
• 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 performed at baseline, after 5 years, and yearly thereafter **(2b/B)**.	**9.75 (0.70)**
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 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 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 ≥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 GC[45] 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. antipshychotics 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/mm^3) 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/mm^3) 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 (± 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

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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

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