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PAPER

Current state of evidence on 'off-label' therapeutic options for systemic lupus erythematosus, including biological immunosuppressive agents, in Germany, Austria and Switzerland – a consensus report

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Systemic lupus erythematosus (SLE) can be a severe and potentially life-threatening disease that often represents a therapeutic challenge because of its heterogeneous organ manifestations. Only glucocorticoids, chloroquine and hydroxychloroquine, azathioprine, cyclophosphamide and very recently belimumab have been approved for SLE therapy in Germany, Austria and Switzerland. Dependence on glucocorticoids and resistance to the approved therapeutic agents, as well as substantial toxicity, are frequent. Therefore, treatment considerations will include 'off-label' use of medication approved for other indications. In this consensus approach, an effort has been undertaken to delineate the limits of the current evidence on therapeutic options for SLE organ disease, and to agree on common practice. This has been based on the best available evidence obtained by a rigorous literature review and the authors' own experience with available drugs derived under very similar health care conditions.

Preparation of this consensus document included an initial meeting to agree upon the core agenda, a systematic literature review with subsequent formulation of a consensus and determination of the evidence level followed by collecting the level of agreement from the panel members. In addition to overarching principles, the panel have focused on the treatment of major SLE organ manifestations (lupus nephritis, arthritis, lung disease, neuropsychiatric and haematological manifestations, antiphospholipid syndrome and serositis).

This consensus report is intended to support clinicians involved in the care of patients with difficult courses of SLE not responding to standard therapies by providing up-to-date information on the best available evidence. *Lupus* (2012) **21,** 386–401.

Key words: adverse events; biological response modifiers; consensus; evidence; off-label treatment; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) represents a severe disease, which may be life-threatening even despite optimized therapy.[1] SLE remains a

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therapeutic challenge because of its great heterogeneity in organ manifestations and variable courses of disease.[2] Dependence on glucocorticoids, toxicity of therapeutic agents used for severe disease manifestations, and resistance to approved immunosuppressive therapy represent considerable challenges.[3]

SLE patients display hyperactivity of the innate and adaptive immune system, including T and B cell abnormalities, overproduction of autoantibodies and disturbed cytokine balance, such as high levels of B cell activating factor of the TNF family (BAFF), interleukin (IL)-6, interferon (IFN)α or tumour necrosis factor (TNF).[4,5] Heterogeneity in the expression of these abnormalities, as well as clinical disparities, differentiates SLE patients from one another.[6] SLE thus represents one of the most variable systemic autoimmune diseases. In addition, there is substantial uncertainty as to which of these immunological findings are of primary versus secondary nature.[7]

As final pathways, however, a variety of autoantibodies and the ensuing immune complexes result in complement activation, cell destruction and tissue inflammation. The course of the resulting disease can vary from subclinical or very mild SLE to life-threatening organ involvement. In particular, it is the organ involvement that mainly defines both prognosis and choice of therapy.

Adding to the complexity of SLE, ethnic background has been shown to influence not only susceptibility to, and severity of, SLE, but also response to certain drugs, such as MMF,[8] rituximab[9] or abatacept.[10] This needs careful consideration when results of globally recruiting clinical trials are compared with open label studies[11,12] or registry data.[13–18] Therefore, results on targeted therapies come with foreseen limitations in SLE.

While an evidence-based approach to therapy is desirable, the actual evidence from controlled trials testing the effectiveness of immunosuppressive therapies in SLE is still extremely limited. No new drugs for SLE were approved for decades and several recent studies have been disappointing.[7] However, very recently, a new drug, belimumab, has been approved by both the Food and Drugs Administration (FDA) and the European Medicines Agency (EMA). Not only is this the first new drug licensed in SLE for decades, but it is also the first biological agent for SLE, which may herald further developments in this regard, one decade after approval of biologics for rheumatoid arthritis (RA) and subsequently also other arthritides. Trial results and limitations will be discussed below.

Before belimumab, only glucocorticoids, chloroquine and hydroxychloroquine, azathioprine and cyclophosphamide had been approved for SLE therapy in Germany, Austria and Switzerland. Although these at least included cyclophosphamide and azathioprine, which are still off label in the US, these drugs will often not achieve sufficient control of the disease and may cause severe, often irreversible, damage and/or pose inacceptable risks.

Therefore, off-label use of medication approved for other indications has to be considered for managing difficult-to-treat SLE patients, and evaluation of these therapeutic options represents the aim of this consensus approach. Novel therapies, such as biological response modifiers, will be seen as an option to treat patients with life- or organ-threatening disease.

In this consensus approach, we tried to delineate the limits of the current evidence on therapeutic options for SLE organ disease, and to agree on common approaches based on the best available evidence and own experience with available drugs derived from a mainly Caucasian population under very similar health care conditions.

Methods

We gathered a group of physicians who have a proven academic track record and long-standing experience in caring for patients with SLE at academic centres in Germany, Switzerland and Austria. All of them have a major focus on clinical and basic research as well as the use of immunosuppressive and biologic agents and came together to develop a consensus statement on the state of evidence regarding off-label use of immunosuppressive and biological medications in SLE, based on the available literature and current clinical experience.

The initial meeting took place in Berlin on 30 August 2010. Subsequently, until 15 November 2010, a systematic literature review of the published English literature on efficacy and safety of off-label therapy in patients with SLE was undertaken to identify relevant data and information. For this review, the following currently available substances were evaluated (in alphabetical order): abatacept, adalimumab, anakinra, certolizumab pegol, cyclosporine, etanercept, golimumab, infliximab, mycophenolate mofetil, rituximab, tacrolimus and tocilizumab.

The search term of the drug was linked to the term (lupus OR sle, NOT review), and this search

was performed on PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez) and the ACR (http://www.rheumatology.org/education/annual/abstracts_general_info.asp#) and EULAR (http://www.abstracts2view.com/eular/) conference abstracts of the last 4 years.

If, for a given (organ-focused) question, publications of several levels of evidence (A–D)[19] were found, the manuscripts with the highest level of evidence were chosen. For example, for rituximab in the first line therapy of lupus nephritis, the randomized controlled trial was primarily reviewed, while open label evidence was the best available for refractory disease. When the evidence was limited to category C, we decided to focus on the publications with larger numbers of patients ($n \geq 40$, if not available $n \geq 20$ or even $n \geq 10$), where feasible. In addition, all evidence contradictory to these larger sample publications was taken into account.

The resulting consensus statements list the drugs in order of the evidence for each of them. Choice of medication will always have to be based on individual factors. Therefore, the statement should not be used independently of the text following the statements. Other than for state of the art therapies and clear recommendations, the word 'may' was always used despite consensus on the appropriate use of these medications in refractory disease.

The manuscript was revised by the authors, and then the recommendations were voted on in the last 2 weeks of January 2011, after which the manuscript was finalized by all authors. According to EULAR standards, all statements were assigned a level of evidence and evaluated in a second step on the level of agreement (scale 0–100% agreement) by each member of the group independently. The votes were received by an epidemiologist (A.S.) of an independent institution (DRFZ Berlin; Germany), who calculated the levels of agreement for each statement (Table 1).

Results

The literature search on abatacept in SLE resulted in only one out of 31 relevant publications.[10] The search on the five available TNF blockers, adalimumab, certolizumab pegol, etanercept, golimumab and infliximab, resulted in 265 publications, of which 15 dealt with the actual use of TNF blockers in SLE, including two series of nine and 13 patients, respectively.[20,21] Moreover, two out of 31 publications on anakinra,[22,23] four of 212 on the use of cyclosporine A,[24–27] nine out of 177 on MMF,[8,28–35] eight out of 184 publications reporting on Rituximab (RTX),[9,11,15,36–40] three out of 49 reports on tacrolimus,[41–43] and finally one out of eight on tocilizumab[44] in SLE were chosen for final evaluation, since they constituted the best representation of the evidence for the given question (Table 2).

Consensus

In its initial session, the consensus group has decided to focus on specific organ systems, the involvement of which commonly necessitates therapy in SLE. For the following main part of this document, we will therefore focus on SLE organ disease, with the exception of SLE skin disease, for which a recent overview exists.[45] We wish to stress that this consensus statement is limited to immunosuppressive medication and explicitly excludes other (non-immunological) therapies, such as blood pressure control or lipid lowering drugs, which often are of central importance for the overall outcome.

In addition to organ-specific options, it also appears worthwhile to shortly reiterate some principles, wherein we are able to refer to EULAR recommendations.[2] It is extremely important that all UV-sensitive patients should avoid sun and UV exposure. Most SLE patients should be treated with antimalarials, low dose glucocorticoids, and vitamin D as initial and/or adjunctive treatment.[2,46]

On the other hand, there is no sufficient evidence that fatigue can be influenced by immunosuppression in the absence of anaemia or any other known causes of fatigue. While extremely common in SLE,[47] fatigue often does not respond sufficiently to measures reducing SLE activity. Nevertheless, recent trials of blocking BAFF (BLISS-52 and 76)[48] and low intensity physical activity[49] have been shown to improve quality of life scores, including fatigue.

As outlined above, several drugs or procedures have been used 'off label' in the attempt to control active SLE that is refractory to licensed therapy. In order to appropriately consider off-label use, it appeared important to delineate the current standard of care per organ system. The following parts will therefore start with a general principle followed by a consensus statement on difficult-to-treat situations, where level of evidence as well as percentage and mean level of agreement are provided. In each paragraph, we will then delineate the actual evidence underlying the respective consensus statement.

1. *Overarching principles*

Severe SLE is a life-threatening condition, which should be treated by physicians trained and experienced in the management of patients with systemic autoimmune diseases. Optimal treatment requires an interdisciplinary approach in a dedicated centre. (D, mean agreement 9.9, range 9–10)

Aims of treatment comprise reduction of disease activity to prevent irreversible organ damage or premature death. Moreover, improvement of QoL and social participation shall be achieved. (D, mean agreement 9.9, range 9–10)

In addition, reduction of substantial risks for adverse effects, particularly those due to glucocorticosteroids and cyclophosphamide, needs to be balanced against the risk/benefit ratio of alternative therapies. (C, mean agreement 9.8, range 9–10)

Treatment goals should be defined together with the patient in a shared decision considering individual aspects of the disease manifestations. (D, mean agreement 9.2, range 7–10)

Untreated SLE regularly is a fatal disease.[50–52] Even under current state of the art therapy, SLE remains a potentially life-threatening, complex, chronic, multisystem disease with variable presentation, course and prognosis.[2] Severe SLE, in particular, harbours a substantial risk of premature mortality. Moreover, longer-lasting disease, even if less active, leads to accrual of damage and increased mortality as compared with the normal population. The overall standardized mortality ratio (SMR) for SLE patients is about 2.4 (95% confidence interval [CI] 2.3–2.5).

As causes of death, high disease activity and major organ involvement dominate in the first years of the disease, while infectious and cardiovascular complications lead in later stages.[53] The current SMR of 2.4 is already a significant achievement, given that the SMR in the 1970s was 5.0, placing SLE in line with malignant lymphoma.

SLE mainly affects women of childbearing age. The incidence of the disease is estimated at 1.5 to 7.6 per 100,000, leading to a prevalence of 20 to 120 cases per 100,000,[54] and is thought to have increased in the past decades. SLE has a negative impact on quality of life (QoL) and is associated with high health care costs and significant productivity loss.

The mean annual medical costs have been calculated to be $16,000 to $24,000 for SLE patients and $13,228 to $34,907 for those suffering from lupus nephritis. Factors associated with increased cost of SLE include long disease duration, high disease activity and damage caused by the disease or its treatment.[55,56]

Arthritis, different types of (sometimes scarring) rashes, serositis, cytopenias of various types, neurological symptoms and nephritis are among the typical organ manifestations caused by the disease. SLE can mimic other diseases, and similarities between SLE manifestations and complications of the disease or the medication used make for challenging differential diagnoses.

Therefore, diagnosis and treatment of SLE should rely on specialized physicians, with training and experience in the management of patients with systemic autoimmune diseases. Optimal treatment requires an interdisciplinary approach, which can often only be provided in specialized centres.[57] SLE treatment aims at sufficient reduction of disease activity to prevent organ damage and premature death. Moreover, improvement of QoL and social participation should be maintained or restored.[58]

Two of the current mainstays of therapy for severe SLE, namely glucocorticosteroids and cyclophosphamide, are associated with substantial adverse effects, damage and mortality. Infections are an important problem and a leading cause of death for SLE patients. Therefore, steroids should be tapered as soon as possible to avoid infectious complications,[59] and reduction in steroids to below 10 mg q.d. is an important goal of immunosuppressive therapy.

In addition to avoiding infections, maintaining fertility in women with SLE, which is severely compromised by higher cyclophosphamide exposure, is of particular relevance in SLE. Treatment goals should be defined together with the patient by shared decision, considering individual life and disease aspects.

2. *Lupus nephritis*

Standard of care using approved medications for patients with proliferative lupus nephritis is treatment with glucocorticoids and pulse cyclophosphamide (such as according to the Euro-Lupus regimen), followed by maintenance therapy with azathioprine. (A, mean agreement 9.3, range 7–10)

In case of contraindications for or intolerance to cyclophosphamide and/or azathioprine, mycophenolate induction or maintenance therapy has been shown non-inferior in randomized controlled clinical trials. (A, mean agreement 9.5, range 6–10)

Patients who do not adequately respond to these therapies may benefit from B cell depletion with rituximab, or from short term TNF blockade,

Table 1 Consensus statements with the attached level of evidence and mean and range of level of agreement, ordered by organ manifestation. (Evidence levels: A randomized controlled trials, B well controlled other trials, C open label trials, D expert opinion)

	Evidence	*Agreement*
1. Overarching principles		
Severe SLE is a life-threatening condition, which should be treated by physicians trained and experienced in the management of patients with systemic autoimmune diseases. Optimal treatment requires an interdisciplinary approach in a dedicated centre.	D	9.9 (9–10)
Aims of treatment comprise reduction of disease activity to prevent irreversible organ damage or premature death. Moreover, improvement of QoL and social participation shall be achieved.	D	9.9 (9–10)
Reduction of substantial risks for adverse effects, particularly those due to glucocorticosteroids and cyclophosphamide, needs to be balanced against the risk/benefit ratio of alternative therapies.	C	9.8 (9–10)
Treatment goals should be defined together with the patient in a shared decision considering individual aspects of the disease manifestations.	D	9.2 (7–10)
2. Lupus nephritis		
Standard of care using approved medications for patients with proliferative lupus nephritis is treatment with glucocorticoids and pulse cyclophosphamide (such as according to the Euro-Lupus regimen), followed by maintenance therapy with azathioprine.	A	9.3 (7–10)
In case of contraindications for or intolerance to cyclophosphamide and/or azathioprine, mycophenolate induction or maintenance therapy has been shown non-inferior in randomized controlled clinical trials.	A	9.5 (6–10)
Patients who do not adequately respond to these therapies may benefit from B cell depletion with rituximab, or from short-term TNF blockade, tacrolimus or immunoadsorption.	C	9.2 (5–10)
Patients with membranous lupus nephritis may also respond to azathioprine or cyclosporine A.	A	9.2 (8–10)
3. Antiphospholipid syndrome (APS)		
For SLE patients with APS, the standard of care is treatment with anticoagulation to avoid subsequent thromboembolic events.	A	9.9 (9–10)
For catastrophic antiphospholipid syndrome, additional intensive immunomodulatory therapy, such as high dose glucocorticoids, IVIG and plasmapheresis, may improve survival.	C	9.4 (7–10)
If standard measures fail, antiphospholipid antibody levels may be lowered by B cell depletion with rituximab or direct removal via apheresis procedures.	C	9.1 (7–10)
4. Neuropsychiatric SLE		
Severe vascular CNS manifestations in SLE patients are commonly caused by atherosclerosis or antiphospholipid syndrome and should then be treated accordingly.	C	9.5 (8–10)
Patients with severe neuropsychiatric lupus not caused by antiphospholipid syndrome or atherosclerosis and not sufficiently responding to high dose glucocorticoid pulse therapy usually benefit from cyclophosphamide therapy.	A	9.5 (5–10)
Given the risk of irreversible damage by active disease, rituximab, intravenous immunoglobulin, and immunoadsorption or plasmapheresis should be considered early for these patients.	C	8.8 (2–10)
5. Lupus arthritis		
The current standard of care for patients with lupus arthritis includes glucocorticoids, antimalarials, azathioprine and methotrexate, although the last is not formally approved.	B	9.8 (9–10)
Patients whose arthritis does not respond to standard of care therapies may benefit from mycophenolate mofetil, and potentially from cyclosporine A or leflunomide.	C	9.0 (6–10)
B cell depletion with rituximab, costimulation blockade with abatacept, and IL-6 receptor blockade with tocilizumab may be helpful in selected refractory patients. It is not advisable to use TNF antagonists or IL-1 blockade in these patients.	C	8.8 (2–10)
6. Haematological manifestations		
The standard of care for severe haemolytic anaemia, leukocytopenia or thrombocytopenia commonly includes glucocorticoids and azathioprine, or, occasionally, cyclophosphamide.	C	9.7 (6–10)
In addition, MMF, cyclosporine A, B cell depletion with rituximab, intravenous immunoglobulin or immunoadsorption may be effective.	C	9.4 (3–10)
For selected patients with severe thrombocytopenia refractory to drug therapy, splenectomy may be considered as a last resort.	C	8.7 (1–10)
TTP is a very uncommon haematological manifestation of SLE. The standard of care is apheresis/immunoadsorption in combination with glucocorticosteroids. In the case of lack of efficacy, the addition of cyclophosphamide or a switch to rituximab may be helpful.	C	9.2 (8–10)
7. Lung disease		
The standard of care for patients with lupus pneumonitis commonly consists of high dose glucocorticoid and cyclophosphamide therapy.	C	9.8 (9–10)
Haemorrhagic alveolitis and refractory disease may respond to antibody removal or B cell depletion with rituximab.	C	9.3 (7–10)
The standard of care for patients with SLE interstitial lung disease mostly relies on (prolonged) pulse cyclophosphamide therapy. Refractory interstitial lung disease may respond to B cell depletion or TNF blockade.	C	9.4 (3–10)
Standard of care treatment of PAH in SLE is based on the ESC/ERS guidelines; immunosuppression with cyclophosphamide should be considered.	C	8.8 (6–10)

(continued)

Table 1 Continued

	Evidence	*Agreement*
8. Serositis		
Serositis mostly responds to standard of care therapy with NSAIDs, glucocorticoids, antimalarials, azathioprine, and in life-threatening cases cyclophosphamide.	C	9.8 (8–10)
In selected cases, methotrexate, MMF, B cell depletion with rituximab, or abatacept may be considered.	C	9.5 (8–10)

APS: antiphospholipid syndrome, CNS: central nervous system, ESC/ERS: European Society of Cardiology and European Respiratory Society, IL: interleukin, IVIG: intravenous immunoglobulin, MMF: mycophenolate mofetil, PAH: pulmonary arterial hypertension, QoL: quality of life, SLE: systemic lupus erythematosus, TNF: tumour necrosis factor, TTP: thrombotic-thrombocytopenic purpura.

tacrolimus, or immunoadsorption. (C, mean agreement 9.2, range 5–10)

Patients with membranous lupus nephritis may also respond to azathioprine, or cyclosporine A. (A, mean agreement 9.4, range 8–10)

For patients with proliferative lupus nephritis, the National Institutes of Health (NIH) regimen of cyclophosphamide pulses has turned an 80% long-term risk of kidney failure into a less than 10% risk,[60] but at the price of high rates of ovarian failure, infections and increased risk for cancer.[61,62] While stopping cyclophosphamide after the induction phase of the NIH regimen was not effective,[63] a switch to either azathioprine or MMF showed benefit.[62]

Without losing efficacy, the cyclophosphamide dose could be further reduced to a total of 3 g in 500 mg pulses administered every other week, using the Euro-Lupus nephritis trial protocol.[64] Therefore, the Euro-Lupus regimen, with its much reduced risk for ovarian failure, may currently constitute the best option in the therapy of proliferative lupus nephritis, at least for Caucasian patients with normal or moderately reduced renal function.

Moreover, alternative effective treatments, and MMF in particular, may gain increasing importance especially for adolescent patients and young adults planning a family. While MMF is not approved for SLE, two randomized controlled clinical trials have shown that induction with MMF is non-inferior to a classical cyclophosphamide induction regimen.[8,28] In addition, post hoc subanalyses on patients of Afro-American and Hispanic descent showed MMF to be superior.[8,28] In countries where SLE patients often come from these ethnic backgrounds, including the US, this has led to widespread use of MMF.

Recently, maintenance therapy using MMF was shown to prevent significantly more flares than maintenance with azathioprine within the Aspreva Lupus Management Study (ALMS) maintenance trial following responders of the ALMS induction study (MMF versus i.v. cyclophosphamide).[30] This effect was seen in both the cyclophosphamide and MMF induction groups, but was somewhat less pronounced after cyclophosphamide.[30] In some contrast, a smaller follow-up study of a Euro-Lupus induction regimen, in which MMF was compared with azathioprine for maintenance, showed no significant difference between the two drugs.[31] There is also evidence that MMF is effective for membranous lupus nephritis.[32,33] Long-term data on lupus nephritis under MMF are still limited.[34]

As an induction therapy, azathioprine was less effective than cyclophosphamide in a randomized controlled trial investigating induction therapy for proliferative lupus nephritis.[65] However, azathioprine probably is effective for membranous lupus nephritis.[66]

Cyclosporine A may be effective in membranous lupus nephritis.[25] In small controlled trials of intermediate duration low dose cyclosporine A has also been found effective as a maintenance therapy after cyclophosphamide[26] and even as an induction therapy.[27] Tacrolimus may also induce remission in membranous lupus nephritis.[43]

While most patients with lupus nephritis will experience a good clinical response or remission with standard therapies, a number of patients will not. Currently, there is insufficient evidence on how to best treat these refractory patients.

Several large case series[14,15,37,67] and registry data[14–18,38,68,69] have reported on successful therapy of such patients with the anti-CD20 antibody rituximab. In addition, a smaller series has shown clear improvement in pathohistological changes of lupus nephritis under the combination of rituximab and cyclophosphamide.[38]

The only randomized controlled trial on rituximab in lupus nephritis performed so far (Lupus Nephritis Assessment with Rituximab [LUNAR]) included no patients who were refractory to standard therapy.[9] This relatively short-term trial of 52 weeks' duration, in which high doses of

Table 2 Best available evidence for various off-label drugs used in SLE

Off-label therapy	*Evidence level*	n *(:*n *control)*	*Ref*	*Result*	*Remarks*
MMF	A (RCT)	184:180	(8)	MMF not superior to CP	Renal induction
	A (RCT)	71:69	(28)	MMF superior to CP	Renal induction
	A (RCT)	73:54	(30)	MMF superior to Aza	Renal maintenance
	A (RCT)	53:52	(31)	MMF not superior to Aza	Renal maintenance
Cyclosporine	A (RCT)	47:42	(24)	Equal to azathioprine	Not organ-defined
	A (RCT)	36:33	(26)	Not significantly worse than Aza	Renal maintenance
	A (RCT)	19:21	(27)	Not significantly worse than CP	Renal induction
	A (RCT)	11:12:12	(25)	Similar induction, more flares than CP	Pure class V (membranous) nephritis
Tacrolimus	C (open label trial)	18	(43)	Response rate 50%	Pure class V (membranous) nephritis
	C (open label trial)	17	(42)	Response rate 70%	MMF refractory nephritis, MMF combination
	C (open label trial)	9	(41)	Response rate 78%	Refractory nephritis
Rituximab	A (RCT)	72:72	(9)	Rituximab + MMF not superior to MMF	Renal induction
	A (RCT)	169:88	(19)	Rituximab + SOC not superior to SOC	Not organ-defined
	C (dose ranging trial)	18	(36)	Most B cell depleters improved	Arthritis, skin
	C (open label trial)	10	(39)	Complete recovery 40% of patients	Refractory NPSLE
	C (open label trial)	7	(38)	Histological and clinical improvement	Refractory nephritis
	C (combined registries)	43	(15)	Improved proteinuria	Refractory nephritis
	C (Registry)	52	(37)	Remission 48% of patients	Refractory nephritis, arthritis, haematology
	C (Registry)	50	(11)	Improvement 89% of patients	Refractory disease
Abatacept	A (RCT)	118:57	(10)	Abatacept not superior to SOC	Possible improvement in arthritis subset
Tocilizumab	C (dose escalation trial)	16	(44)	8/15 patients improved	Arthritis ($n = 7$)
Infliximab	C (open label trial)	13	(21)	Prolonged renal response 67% of patients	Refractory nephritis, arthritis, ILD
	C (open label trial)	13	(20)	Improved proteinuria in 67% of patients	Refractory nephritis
Anakinra	C (open label trial)	4	(23)	No prolonged therapeutic effect	
	C (open label trial)	3	(22)	No prolonged therapeutic effect	

Aza: azathioprine, CP: cyclophosphamide, ILD: lupus interstitial lung disease, MMF: mycophenolate mofetil, NPSLE: neuropsychiatric SLE, RCT: randomized controlled trial, SOC: standard of care. For RCTs numbers of the arm of the respective off-label drug and control arms are given separately.

glucocorticoids were given per protocol also in the control group, found no significant benefit of the combination of MMF (here defined as standard of care) with additional rituximab as compared with MMF alone. In addition to the potentially suboptimal combination with MMF instead of cyclophosphamide, and other possible shortcomings of the protocol,[70,71] this trial targeted a patient population likely to respond well to other agents. While new randomized controlled trials may change this picture in the future, this trial still represents the best available evidence on rituximab in patients with newly diagnosed lupus nephritis. There is currently no sufficient evidence to contradict this trial and demonstrate that addition of rituximab provides benefit at this stage of the disease.

In contrast, there are no controlled studies available on patients with lupus nephritis refractory to cyclophosphamide (or other standard of care agents in the case of cyclophosphamide contraindications). Current experience suggests that rituximab is a valid option for these patients. Rituximab has been found associated with Progressive multifocal leukoencephalopathy (PML), which is a serious concern. However, PML is well known to occur in SLE without such therapy, and the incidence estimate of approximately 1:4000 was still considerably lower than with other medications associated with PML.[72]

Short-term TNF blockade may be another option for patients with refractory lupus nephritis. In a small series of nine patients with refractory lupus nephritis, six responded to an induction regimen with four infusions of the anti-TNF antibody infliximab at a dose of 5 mg/kg and in combination with azathioprine.[21] Most of these patients had been refractory to cyclophosphamide; one of them had previously not responded to rituximab in addition to standard therapy. Proteinuria was markedly reduced, and most patients who responded achieved a long-lasting remission. In addition, several other small series reported on patients with lupus nephritis responding to TNF blockade.[20,73,74] In contrast to long-term TNF blockade, which appeared associated with life-threatening events, short-term induction therapy with infliximab

appeared to have an acceptable safety profile in SLE.[21] Although there is still limited experience, TNF blockade may constitute an alternative option for patients with refractory lupus nephritis.

Recent open label data also suggest that tacrolimus alone, or in combination with MMF, may constitute an additional therapeutic option for patients with refractory lupus nephritis class III, IV or V. Two open label trials and one observational study investigating tacrolimus monotherapy or combination therapy with MMF for 12 months up to 5 years in 33 patients revealed response rates between 57 and 78%, with complete remission achieved for 14 to 35% of patients.[41,42,75] However, open questions regarding safety of combination therapy with MMF need to be addressed in further clinical trials.

Under circumstances in which most immunosuppressive medication cannot be used, such as in pregnancy, immunoadsorption may improve proteinuria and overall disease activity and therefore constitutes a rescue option.[76]

3. *Antiphospholipid syndrome (APS)*

For SLE patients with APS, the standard of care is treatment with anticoagulation to avoid subsequent thromboembolic events. (A, mean agreement 9.9, range 9–10)

For catastrophic antiphospholipid syndrome, additional intensive immunomodulatory therapy, such as high dose glucocorticoids, IVIG and plasmapheresis may improve survival. (C, mean agreement 9.4, range 7–10)

If standard measures fail, antiphospholipid antibody levels may be lowered by B cell depletion with rituximab or direct removal via apheresis procedures. (C, mean agreement 9.1, range 7–10)

APS is a classical example of autoantibody-mediated autoimmunity,[77,78] interfering with clotting factors, endothelial cells and platelets, resulting in vascular occlusions under certain predisposing conditions. Treatment today essentially consists of anticoagulation and/or platelet inhibition.[79–81] Hydroxychloroquine, which should be administered to most SLE patients,[2] may also help to reduce thrombotic risks.[82,83]

However, immunosuppression has so far not been shown to be beneficial in APS. The one exception is catastrophic antiphospholipid syndrome ('thromboembolic storm'), in which glucocorticoids combined with intravenous immunoglobulin, plasmapheresis or immunoadsorption may improve survival.[84] Moreover, B cell depletion may diminish antiphospholipid antibodies,[85] and immunoadsorption may directly reduce these antibodies.[86] While this may provide a rationale for patients not responding to high level anticoagulation, clinical benefit remains to be convincingly shown.

4. *Neuropsychiatric SLE*

Severe vascular CNS manifestations in SLE patients are commonly caused by atherosclerosis or antiphospholipid syndrome and should then be treated accordingly. (C, mean agreement 9.5, range 8–10)

Patients with severe neuropsychiatric lupus not caused by antiphospholipid syndrome or atherosclerosis and not sufficiently responding to high dose glucocorticoid pulse therapy usually benefit from cyclophosphamide therapy. (A, mean agreement 9.5, range 5–10)

Given the risk of irreversible damage by active disease, rituximab, intravenous immunoglobulin and immunoadsorption or plasmapheresis should be considered early for these patients. (C, mean agreement 8.8, range 2–10)

Lupus vasculitis within the central nervous system (CNS) is an uncommon event, and most strokes are either caused by (premature) atherosclerosis or by antiphospholipid antibodies.[19] In either case, the appropriate standard measures should be taken, but immunosuppression is unlikely to convey additional benefit.

Although relatively rare, CNS vasculitis can occur in SLE, as does directly autoantibody-mediated nerve cell degeneration or reversible neuropsychiatric symptoms. In case of (non-APS) autoimmune processes, high dose glucocorticoid pulses are standard, and cyclophosphamide has been shown to confer additional benefit.[87]

In the case of refractory disease and in critical situations where irreparable damage is a serious concern, rituximab, presumably best in combination with cyclophosphamide, may currently be the best option.[39,88,89] Although there are no controlled trials, case series suggest that rituximab may be highly efficacious under these circumstances. Peripheral neuropathy, in particular, may respond to intravenous immunoglobulin (IVIG).[90,91] Plasmapheresis and immunoadsorption have also been occasionally reported to be beneficial.[92,93]

5. *Lupus arthritis*

The current standard of care for patients with lupus arthritis includes glucocorticoids, antimalarials, azathioprine and methotrexate, although the latter is not formally approved. (B, mean agreement 9.8, range 9–10)

Patients, whose arthritis does not respond to standard of care therapies, may benefit from mycophenolate mofetil, and potentially from cyclosporine A or leflunomide. (C, mean agreement 9.0, range 6–10)

B cell depletion with rituximab, costimulation blockade with abatacept, and IL-6 receptor blockade with tocilizumab may be helpful in selected refractory patients. It is not advisable to use TNF antagonists or IL-1 blockade in these patients. (C, mean agreement 8.8, range 2–10)

Arthritis is a relatively common problem in SLE. If antimalarials are not effective, methotrexate is the best supported approach,[94,95] but there is also some evidence that azathioprine, mycophenolate mofetil and cyclosporine may be beneficial,[24,29] and less evidence that leflunomide may be helpful.[96] Severe, refractory lupus arthritis may still constitute a significant problem, for the treatment of which there is no adequate evidence.

Based on RA experience, the use of rituximab in lupus arthritis appears attractive. Indeed, a dose ranging study showed benefit in patients after B cell depletion,[36] and case series suggest that lupus arthritis commonly goes into remission under such therapy.[11,37] In addition, abatacept has been found to have an effect on lupus arthritis.[10] While a new BILAG A arthritis flare was only seen in 36.5% of the SLE patents treated with abatacept as compared with 62.5% in the placebo group, the primary endpoints of this trial were not met.

In an open label trial, the anti-IL-6 receptor antibody tocilizumab showed benefit for lupus arthritis.[44] In contrast, IL-1 blockade has apparently no clear longer-term benefit in lupus arthritis.[22,23] TNF blockade appears to provide only short-term improvement, has to be given long-term and is then associated with significant adverse events.[21] The mammalian target of rapamycin (mTOR) inhibitor rapamycin has also been reported beneficial in severe lupus arthritis in a small retrospective analysis.[97]

6. *Haematological manifestations*

The standard of care for severe haemolytic anaemia, leukocytopenia or thrombocytopenia commonly includes glucocorticoids and azathioprine, or, occasionally, cyclophosphamide. (C, mean agreement 9.7, range 6–10)

In addition, MMF, cyclosporine A, B cell depletion with rituximab, intravenous immunoglobulin, or immunoadsorption, may be effective. (C, mean agreement 9.4, range 3–10)

For selected patients with severe thrombocytopenia refractory to drug therapy, splenectomy may be considered as a last resort. (C, mean agreement 8.7, range 1–10)

Thrombotic-thrombocytopenic purpura (TTP) is a very uncommon haematological manifestation of SLE. The standard of care is apheresis/immunoadsorption in combination with glucocorticosteroids. In case of lack of efficacy, the addition of cyclophosphamide or a switch to rituximab may be helpful. (C, mean agreement 9.5, range 8–10)

Anaemia of chronic disease, lymphocytopenia and mild thrombocytopenia are very common in SLE. In contrast, severe thrombocytopenia, leukocytopenia, and aplastic or haemolytic anaemia are uncommon, but potentially life-threatening, SLE manifestations. In most cases, these problems will be controlled by relatively high doses of glucocorticoids. However, longer-term control may be difficult.

Azathioprine is the most common choice in these situations, based on long-term experience and largely observational evidence for its use.[98] If it is unsuccessful or not tolerated, MMF and cyclosporine A are recommended based on indirect evidence from trials and successful cases and/or case series.[29,99–102]

If these standard therapies are not effective, patients may respond to cyclophosphamide.[103,104] Cases and case series on patients with refractory thrombocytopenia or haemolytic anaemia suggest efficacy of B cell depletion.[105,106] In addition, there are reports on IVIG[107–110] and immunoadsorption.[76]

Splenectomy may be effective for SLE thrombocytopenia, but does not confer benefit to all patients[111,112] and is associated with relevant procedure-related morbidity and even mortality.[113] In addition, functional hyposplenism or even asplenia may be an underrecognized condition in SLE patients,[114] potentially resulting in a high risk of both opportunistic infection and unsuccessful outcome after splenectomy.

Hence, in contrast to idiopathic TTP, in which splenectomy is considered equal to medical second line treatments after failure of glucocorticosteroids, IVIG or anti-D therapy,[115] all other therapeutic options should be evaluated before considering splenectomy in SLE patients. There are so far no studies directly addressing the use of thrombopoietin agonists (eltrombopag, romiplostim) in SLE patients with severe thrombocytopenia.

For TTP associated with SLE, glucocorticoids plus plasmapheresis against fresh frozen plasma (or immunoadsorption) are standard of care.

In case of inefficacy, this therapy may be combined with cyclophosphamide (or vincristine),[116,117] or switched to rituximab, which was found effective in case series and individual cases.[118–122] SLE-associated TTP is associated with higher mortality than other forms of TTP; hence, a more aggressive treatment approach, including rituximab, is seen as justified.[119,121]

7. *Lung disease*

The standard of care for patients with lupus pneumonitis commonly consists of high dose glucocorticoid and cyclophosphamide therapy. (C, mean agreement 9.8, range 9–10)

Haemorrhagic alveolitis and refractory disease may respond to antibody removal or B cell depletion with rituximab. (C, mean agreement 9.3, range 7–10)

The standard of care for patients with SLE interstitial lung disease mostly relies on (prolonged) pulse cyclophosphamide therapy. Refractory interstitial lung disease may respond to B cell depletion or TNF blockade. (C, mean agreement 9.4, range 3–10)

Standard of care treatment of pulmonary arterial hypertension (PAH) in SLE is based on the ESC/ERS guidelines; immunosuppression with cyclophosphamide should be considered. (C, mean agreement 8.9, range 6–10)

Both the acute course of lupus pneumonitis and the more smouldering course of SLE interstitial lung disease are rare, life-threatening manifestations. Lupus pneumonitis will primarily be treated with high dose glucocorticoid pulses and, after infection has been excluded, cyclophosphamide in essentially all refractory cases.[123] Alveolar haemorrhage is seen as an indication for additional plasma exchange.[124–126] More recent case reports suggest that rituximab also may provide benefit in these conditions.[21,127,128]

Interstitial lung disease is commonly treated with cyclophosphamide pulse therapy.[129,130] When such standard therapy fails, case reports suggest the efficacy of rituximab[131,132] or infliximab.[21]

So far, there is limited evidence distinguishing pulmonary arterial hypertension (PAH) in SLE from idiopathic PAH, and treatment follows the guidelines of the European Society of Cardiology and European Respiratory Society.[133,134] However, as also mentioned in these guidelines, immunosuppression with glucocorticoids and cyclophosphamide may be effective in SLE PAH, as long as it is not due to APS-induced pulmonary embolism.[135,136]

8. *Serositis*

Serositis is mostly responding to standard of care therapy with NSAIDs, glucocorticoids, antimalarials, azathioprine, and in life-threatening cases cyclophosphamide. (C, mean agreement 9.8, range 8–10)

In selected cases, methotrexate, MMF, B cell depletion with rituximab, or abatacept may be considered. (C, mean agreement 9.5, range 8–10)

Serositis (pericarditis, pleuritis, less likely peritonitis) is a common complication of SLE flares that usually responds to NSAIDs, glucocorticosteroids or hydroxychloroquine.[137,138] Occasionally, immunosuppressants such as azathioprine or, in the rare life-threatening refractory case, cyclophosphamide may be required.[139]

Case reports suggest that rituximab provides benefit in serositis.[140,141] In addition, infliximab was found effective in short-term treatment of serositis in case reports.[142] Abatacept may be another option for patients with refractory SLE serositis, based on reduced severe serositis flares in abatacept-treated patients.[10]

Stem cell transplantation and other alternative rescue options

Immunoablation followed by autologous haematopoietic stem cell transplantation (ASCT) may be a viable option for patients with severe SLE refractory to all conventional immunosuppressive therapies.[143,144] Approximately 200 ASCTs for SLE have been reported worldwide. ASCT can achieve sustained clinical remissions associated with qualitative immunological changes not seen with other forms of therapy. However, the immunoablative regimen leads to a significant risk of transplant-related mortality,[144] stressing the importance of careful patient selection.

Therapeutic apheresis can be considered an emergency option in acute disease phases, such as in CNS vasculitis or haemorrhagic pneumonitis, in patients with active disease in whom immunosuppression is limited or contraindicated (concomitant infections, pregnancy), and in patients with cryoglobulinaemia or hyperviscosity.[145] Plasma exchange is standard therapy in TTP and haemolytic uraemic syndrome (HUS), which can occur in SLE.[146] Immunoadsorption is an alternative to plasma exchange.[76]

Case reports and a few open studies also support the role of IVIG as a salvage therapy in SLE.[147] In addition, a very small controlled trial found IVIG effective for maintaining remission of lupus nephritis.[148] IVIG mainly comes into consideration

in active patients with limitations in using immunosuppressive drugs.

Emerging therapies

There are a number of emerging therapeutic modalities for SLE, which, in Europe, are not yet available for any disease and are therefore out of the scope of this consensus.

Belimumab is a fully human monoclonal antibody that binds to soluble BLyS (B lymphocyte stimulator) and inhibits its biologic activity. Two pivotal belimumab Phase III trials (BLISS-76 and BLISS-52) have included SLE patients with antibody positive (antinuclear antibody level$\geq$1:80 and/or anti-double-stranded DNA [anti-dsDNA] $\geq$30 IU/ml) and clinically active (SLEDAI score $\geq$6) disease on stable standard care therapy.[149,150] Belimumab was generally well tolerated in both studies, with the overall adverse event (AE) rates comparable between the belimumab and placebo groups otherwise receiving standard of care.

The primary endpoint of both studies was defined by the SLE Responder Index (SRI), where patient response is based on an improvement of $\geq$4 points in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) SLEDAI score, with no clinically significant BILAG worsening and no clinically significant worsening in physician global assessment. Both clinical trials reached their primary endpoint at 52 weeks. Subanalysis suggested efficacy for musculoskeletal and mucocutaneous involvement. The European/US BLISS-76 study has not yet been published, which precludes final conclusions. Belimumab has recently been approved by both the FDA and the EMA as a new therapeutic option in the treatment of SLE. While this is a big step forward, we will yet have to see for which organ manifestations this novel biological will change the standard of therapy, as soon as it is actually available, and as soon as additional trials on renal and CNS involvement have been performed.

While there are many other drugs in evaluation for SLE, none of these development programmes are advanced enough to likely obtain approval in the next few years. Nevertheless, several of these therapeutics may have the potential for such approval. Atacicept (TACI-IgG), which inhibits both BLyS and Proliferation Inducing Ligand (APRIL),[151,152] is currently being tested in phase II/III randomized studies in SLE and lupus nephritis. Epratuzumab, a non-depleting humanized antibody that targets CD22 on B cells,[153] will likewise undergo phase III testing. In addition, antibodies against IFNα, namely sifalimumab (MEDI-545) and rontalizumab,[154,155] are being evaluated in controlled clinical trials of advanced clinical development.

Discussion

While clinical studies in SLE have clearly improved our knowledge base for treating SLE patients, it would be fallacious to convey the picture that all SLE patients with severe organ disease can currently receive adequate care based on sufficient evidence. Rather, for many of these patients, therapy will have to be based on current understanding of SLE pathophysiology and limited clinical experience.

Indeed, while some of the therapeutic approaches have not been proven efficacious in randomized controlled clinical trials, case series and/or clinical experience have shown repeatedly that they are apparently effective. Therefore, it would appear unethical to withhold such therapy in severe disease where other therapeutic options have failed and effective approved therapeutic alternatives are unavailable.

We have therefore summarized the available evidence and its limitations. It was our aim to list the current consensus on approved and class I evidence based treatment options to better define patients for whom such options are not available and off-label therapy may have to be used. For these situations, we have tried to reach consensus based on the current knowledge on off-label therapeutic options for SLE organ manifestations, which mainly define the therapeutic choices.

For the time being, complementing the additional efforts on informed consent and documentation inherent in off-label use, we are clearly in favour of registries documenting these therapies. In fact, patients undergoing off-label therapies should be enrolled in registries to assess not only efficacy but also safety, since potential rare adverse effects, such as PML or *Pneumocystis jirovecii* pneumonia, which could be related to these therapies, will need to be recorded.

It is an important but unavoidable limitation of our approach that several of the consensus statements in this document will not be directly transferable to all health care systems. Specifically, differences both in the drugs approved for SLE and in the way off-label therapy is handled within a particular health care system will impact on decisions. The other apparent limitation we face lies in the fact that the evidence presented is still limited. However, we have presented the available evidence,

discuss the respective limitations, and believe that the statements represent the current standard of care in our countries, based on the limited available evidence. Finally, the EMA has just approved belimumab for SLE, after the first submission of this manuscript, and it should soon be available. The impact of this welcome addition to our armamentarium will have to be seen in the coming years. Specifically, there is only limited information published on differential effects of this drug on various organ manifestations of SLE.

It is obvious that this statement will have to be amended as soon as new information becomes available. Moreover, we sincerely hope that, over time, the vast gap in evidence will be filled piece by piece.

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