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The SLE review series: working for a better standard of care

Systemic lupus erythematosus diagnosis and management

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Abstract

SLE presents many challenges for clinicians. The onset of disease may be insidious, with many different symptoms and signs, making early and accurate diagnosis challenging. Tests for SLE in the early stages lack specificity; those that are useful later often appear only after organ damage is manifest. Disease patterns are highly variable; flares are not predictable and not always associated with biomarkers. Children with SLE may have severe disease and present special management issues. Older SLE patients have complicating co-morbid conditions. Therapeutic interventions have improved over recent decades, but available drugs do not adequately control disease in many patients, and successful outcomes are limited by off-target effects; some of these become manifest with longer duration of treatment, now in part revealed by improved rates of survival. Despite all of these challenges, advances in understanding the biological basis of SLE have translated into more effective approaches to patient care. This review considers the current state of SLE diagnosis and management, with a focus on new approaches and anticipated advances.

Key words: antinuclear antibodies, autoantibodies, biological therapeutics, classification criteria, corticosteroids, hydroxychloroquine, immunosuppressive therapy, lupus nephritis, systemic lupus erythematosus

Rheumatology key messages

- Although lupus commonly affects young women, other demographic groups are affected and require special considerations.
- The protean presentations of lupus confound accurate early diagnosis and reliable, predictive biomarkers are needed.
- Optimization of lupus treatments requires a personalized approach, assessing risks and benefits in each patient.

Introduction

SLE is a challenging condition that presents unique issues in diagnosis and management. Patients with SLE present in many different ways and therefore may first encounter the medical system in a number of different clinics, including dermatology, nephrology, neurology, haematology or rheumatology, in both adult and paediatric care settings (Fig. 1). Screening tests for SLE are not always useful. The ANA test is present in a significant proportion of normal individuals and lacks specificity or prognostic value. Recognition of SLE manifestations requires a provider who is trained in its many guises, and specialized clinics for SLE care may best optimize treatment approaches. This review of diagnosis and management of SLE focuses on where the field is now and what changes might be anticipated in the future.

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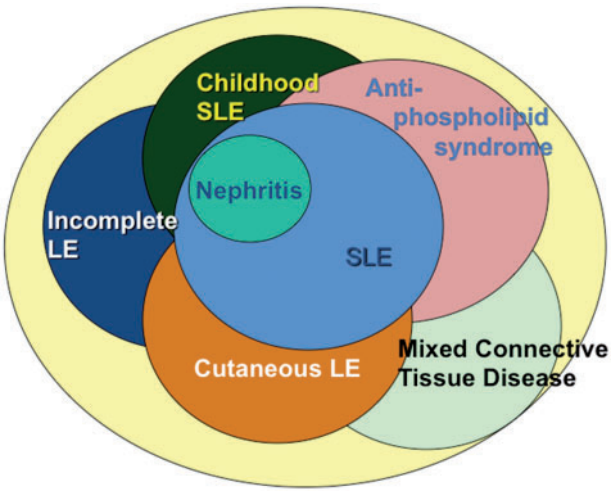
Diagnosis

Classification criteria

The diagnosis of SLE is based on a combination of clinical manifestations, laboratory findings, serology and histology of affected organs (usually skin and kidney). Classification criteria for SLE are used mainly to ensure that patients are comparable in research studies, rather than as diagnostic criteria in routine clinical care. This has evolved from the American Rheumatism Association 1982 criteria [1] and the ACR 1997 criteria [2] to the SLICC 2012

Fig. 1 Heterogeneity of lupus syndromes



SLE is one component of the lupus spectrum. Adult or paediatric patients with nephritis also have SLE, but other lupus syndromes incompletely overlap with SLE itself. Incomplete lupus and cutaneous LE may be subsets that include individuals who will eventually develop SLE. MCTD has distinct elements outside of the usual lupus spectrum, such as erosive arthritis. Anti-phospholipid syndrome may exist as a separate entity or may be part of SLE.

criteria [3]. The SLICC 2012 criteria set has been shown to be more sensitive than the ACR 1997 criteria, to be applicable in childhood-onset SLE and in those with early disease and to be usable in clinical practice [4].

The classification of LN evolved from the World Health Organization 1995 classification [5] to the International Society of Nephrology/Renal Pathology Group 2003 classification [6]. In the SLICC 2012 classification for SLE, biopsy-proven LN plus positive ANA or anti-dsDNA is sufficient to fulfil SLE classification criteria.

In 1999, the ACR developed a standardized nomenclature for NPSLE [7], which was subsequently validated. However, the prevalence of NPSLE has been difficult to establish. The 19 syndromes in the ACR list include common problems, such as headache, which have a high likelihood of being unrelated to the underlying disease. Furthermore, the pathogenesis of most NPSLE syndromes remains obscure and may be multifactorial, so associations with autoantibodies or other putative biomarkers are not well established [8]. In addition, NPSLE syndromes may mimic those seen in APS [9] and SS [10].

Cutaneous lesions occur in up to 85% of patients with SLE and are the first sign in up to 28%. Cutaneous lupus erythematosus is classified into acute, subacute, chronic and intermittent lupus erythematosus [11, 12]. In 2004, the European Society of Cutaneous Lupus Erythematosus was founded to achieve a general consensus on evidence-based clinical standards for disease assessment [13]. The Revised Cutaneous Lupus Erythematosus Disease Area and Severity Index is a validated instrument used in clinical practice and clinical trials to score activity and damage [14].

Incomplete lupus, early SLE or preclinical lupus

Patients with early SLE who do not fulfil the classification criteria for SLE may need to be treated early as for SLE should there be disease progression. These would be patients who would otherwise have been classified as incomplete lupus erythematosus [15]. Clinical judgement is needed to ensure the fine balance between overdiagnosing SLE and underdiagnosing patients with early disease who may progress rapidly. Incomplete lupus erythematosus is distinguished from patients with preclinical disease [16], who have autoantibodies but no clinical abnormalities.

Childhood (juvenile)-, adult- and late-onset lupus

Childhood-onset SLE, defined as onset before 18 years of age, often presents with fever, constitutional symptoms, lymphadenopathy, haemolytic anaemia, thrombocytopenia, NPSLE and LN [17–19]. The disease course is generally more severe than in older patients and may take longer to remit than adult SLE. The SLICC 2012 classification has been validated in childhood-onset SLE [20].

Late-onset SLE is usually defined as onset after 50 years of age. Atypical presentations may contribute to longer delay before diagnosis, especially where the presence of co-morbidities with ageing confound the diagnosis; for example, presence of chronic kidney disease from type 2 diabetes mellitus, cognitive impairment from cerebrovascular disease and sicca symptoms. Most studies have shown a lower frequency of cutaneous manifestations [21], LN and NPSLE, but higher frequency of pulmonary involvement, serositis and peripheral neuropathy [22, 23] in late-onset SLE.

Clinical course and phenotype

Several different clinical courses of SLE have been described. These may be used to stratify and prognosticate different patient profiles, as follows: clinically active,

serologically quiescent [24]; serologically active, clinically quiescent [25], defined as $\geqslant$2 years without clinical activity, with persistent serological activity and off CSs/immunosuppressives; serologically quiescent, clinically quiescent [26]; monophasic illness; relapsing–remitting disease; persistently/chronic active disease [27–29]; prolonged clinical remission (>5 years) [30]; and prolonged complete remission on no treatment (including stopping HCQ) [30, 31].

The pattern may be dependent on different genetics, time to initiation of treatment, extent of organ involvement, types of induction therapies given, use of HCQ, age, medication adherence and psychosocial factors affecting disease control. Prolonged remission is an infrequent outcome, and patients need to be followed for flares at regular intervals. To date, there are no validated biomarkers available to characterize each of these patient subsets.

New approaches to diagnosis, classification and prediction

The protean manifestations of SLE complicate any unified approach to diagnostic testing. SLE is heterogeneous, and many different pathways contribute to disease expression [32]. The unmet needs in terms of diagnostic biomarkers include biomarkers that would be predictive of disease onset or identify early disease stages, as well as biomarkers that have prognostic value, especially in terms of predicting flares or new onset of organ involvement [33]. Development of biomarkers that identify pathogenetically distinct subsets is needed to improve approaches to clinical trials by matching interventions with appropriate immunological targets.

Expanding measurements of candidate biomarkers to large-scale platforms with appropriate analytical capabilities has potential to provide much more information about subsets of patients. These approaches can be used with arrays for gene expression, autoantibodies in different immunoglobulin classes and soluble mediators, such as chemokines and cytokines [34, 35]. Recent analyses in a longitudinal cohort of paediatric SLE patients demonstrated the feasibility of using relatively small numbers of expressed gene transcripts to identify subsets of patients that have different disease features [36]. The plasmablast signature showed the highest correlation with disease activity, and a switch to a neutrophil signature may take place prior to overt nephritis; if the signature change were detected early, it might be predictive of this organ-damaging manifestation.

Another newer marker is the measurement of erythrocyte-bound complement activation products, which are correlated with disease activity measures and may be more sensitive than the usual measures of serum complement proteins 3 and 4 [37].

Management

In routine clinical care [38], assessment and monitoring of the SLE patient includes the following: disease status (activity, end-organ dysfunction and damage); co-morbid conditions (e.g. screening for cardiovascular risk factors such as hyperlipidaemia, diabetes mellitus, osteoporosis and malignancy); medication safety (e.g. immunosuppressive drug adverse reactions, HCQ eye screening); preventive health (e.g. annual immunizations); reproductive health (adults and adolescents); and child/adolescent health (e.g. transition of care to adult services).

These have been developed into clinical quality indicators by the ACR [39] and EULAR [40] for routine care, reproductive health [41] and child health [42]. Although several clinical practice guidelines for monitoring and treatment of SLE exist, the methodological quality, scope and recommendations vary [43].

Disease monitoring

Routine clinical care

Disease activity is monitored using a combination of history, targeted physical examination and laboratory tests of haematology, biochemistry, urinalysis, acute phase reactants (ESR or CRP), complement C3 concentrations and anti-dsDNA titres [38].

Outcome measures of disease activity and damage

Commonly used, validated disease activity indices used to assess SLE disease activity in adults, mainly in clinical trials, include the SLAM, SLEDAI and BILAG. Damage is quantified using the SLICC/ACR Damage Index or SDI [44]. The treatment target in SLE should be to achieve disease remission or low disease activity [45, 46]. There have been several definitions for remission in SLE, including SLEDAI <2 and Lupus Low DAS. Lupus Low DAS comprises the following: SLEDAI-2K $\leqslant$4, with no activity in major organ systems; no new lupus disease activity compared with the previous assessment; Safety of Estrogens in Lupus Erythematosus: National Assessment (SELENA)-SLEDAI physician global assessment (scale 0–3) $\leqslant$1; current prednisolone (or equivalent) dose $\leqslant$7.5 mg daily; and well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents. All global measures of disease activity have been found to be reliable and valid for use in children and adolescents with SLE [47]. The SDI is, however, unable to capture some forms of damage that are unique to children and adolescents, namely growth failure and delayed puberty, which necessitates use of the modified paediatric version.

Lupus flares

Disease flares may occur while on treatment, during tapering of medications or as a result of patient non-adherence. Significant flares are usually associated with the need to make changes in medications. Triggers for flares include the following: infections; ultraviolet irradiation; medications such as quinidine, hydralazine and procainamide [48]; and pregnancy [49]. Low-dose oestrogen/progestogen-containing oral contraceptive pills and hormonal replacement therapy have not been shown to be associated with severe SLE flares [50, 51]. However, ovulation induction therapy has been associated with new

onset of SLE [52]. Non-adherence with prescribed medications may be because of concerns about adverse drug reactions, costs or different health beliefs leading to patient–physician discordance [53], and may result in the need for hospitalization and acute care [54]. Flares can be quantified using the SELENA-SLEDAI flare index and the BILAG-2004 [48]. Predictors of flare include rising anti-dsDNA antibody titres, proteinuria and CRP and B lymphocyte stimulator levels [55].

Special groups

Childhood-onset/adolescent SLE

Patients with childhood-onset SLE face medical and psychosocial needs that are distinct from those of adults [56, 57]. Medical issues include the effects on growth and development. Sexual health and fertility issues include the potential effects of medications on fertility, pregnancies and birth control methods. Childhood vaccinations may be missed, including viral vaccines such as measles, mumps, rubella, oral poliomyelitis and varicella. HPV vaccination to prevent cervical cancer should also be recommended [58]. Adolescents additionally face developmental tasks, such as the need for independence, self-advocacy, educational attainment and employment issues. Transition clinics are useful in transiting teenagers to adult care [59, 60].

Pregnancy

Most women with SLE have successful pregnancies. However, all SLE pregnancies require close monitoring, as flares may occur during any trimester, with potential for harm to the mother and fetus [61, 62]. Prior to conception, it is recommended that SLE be quiescent for at least 6 months, and potentially teratogenic drugs should be discontinued [63]. Low disease activity should be confirmed with laboratory tests. Anti-Ro/La should be measured to assess the risk of congenital heart block and neonatal lupus upon delivery [64]. aPL should be measured, because spontaneous fetal losses and intrauterine growth retardation can be minimized with low-dose aspirin and, possibly, low-molecular-weight heparin if these test positive [65]. SLE disease parameters such as anaemia, ESR and complement levels may be altered. SLE flare during pregnancy may mimic non-SLE complications in pregnancy, a notable one being pre-eclampsia.

Late-onset/elderly SLE

Late-onset SLE patients, particularly those aged 60 years and above, may have developed organ dysfunction from age-related co-morbidities such as macular degeneration, chronic kidney disease, osteoporosis and cardiovascular disease [22, 23]. This may limit the use of certain medications, such as HCQ, in those with diabetic proliferative retinopathy, or where doses of medications such as CYC may have to be attenuated. Concomitant osteoporosis may necessitate a more rapid tapering of high-dose glucocorticoids. Other geriatric syndromes [66], such as functional decline, falls, delirium and cognitive impairment, may impact the pharmacological and non-pharmacological management of SLE. Differentiating NPSLE from other causes of delirium in the elderly may be challenging [67]. Immunization against influenza and pneumococcal infection should be actively recommended in all elderly patients, as well as in younger patients who are on or who are starting immunosuppressants [68]. Varicella zoster vaccination has a potential role in patients aged >60 years [69, 70].

Monitoring co-morbidities

Cardiovascular disease

Premature atherosclerosis is an important cause of morbidity and mortality in SLE [71, 72]. Traditional risk factors that have been found to be independent predictors for coronary heart disease include age, male sex, arterial hypertension, dyslipidaemia and smoking. Disease-related factors include disease activity and duration, cumulative damage, aPL, high-sensitivity CRP and renal disease. CSs have been associated with increased coronary heart disease risk, whereas antimalarials are protective. Carotid ultrasonography may be predictive of cardiovascular events in selected high-risk patients [73].

Metabolic syndrome

Metabolic syndrome is a clustering of cardiovascular risk factors associated with insulin resistance and an increased risk of future type 2 diabetes mellitus and cardiovascular disease [74]. This syndrome has a relatively high prevalence in adults with SLE [75]. Young, premenopausal females with SLE show a 4-fold higher frequency of metabolic syndrome than matched controls [76]. SLE patients with metabolic syndrome have higher SLEDAI scores and cumulative prednisone dose than those without the syndrome. Chloroquine use appears to have a protective effect [76]. Obesity in childhood-onset SLE may contribute to the development of metabolic syndrome over time [77].

Osteoporosis and vitamin D

Adult SLE patients are at risk of gluococorticoid-induced osteoporosis, with postmenopausal females at risk of both gluococorticoid-induced osteoporosis and postmenopausal osteoporosis [78]. Current guidelines on monitoring bone mineral density depend on risk factors in addition to glucocorticoid dose. Indications for initiation of osteoporosis treatment apply to SLE patients as for other patients with gluococorticoid-induced osteoporosis [79] and postmenopausal osteoporosis. The risk of bisphosphonate-induced adverse effects with long-term use, such as atypical femoral fractures [80] and osteonecrosis of the jaw, have to be weighed against the benefits of ongoing treatment [81].

SLE patients who need constantly to use sun protection are at risk for vitamin D deficiency/insufficiency. Although associations of vitamin D deficiency with increased SLE disease activity, increased cardiovascular disease, fatigue and bone health in SLE have been described [82],

Table 1 Medications used in the treatment of SLE

Class	Drug	Indication in SLE	Comments on use	References
Antimalarial	HCQ	All patients without allergy or other contraindication	Requires regular retinal monitoring	[87–100]
	Chloroquine	Patients without good response to HCQ	Relatively high risk of retinal damage	[99]
CS	Methylprednisolone	High dose i.v. in crises	Limit use to short courses	[102, 103]
	Prednisone	Patients with active manifestations	Aim for lowest effective dose	[104–106]
Immunosuppressant	AZA	Nephritis, other significant organ involvement	Safe in pregnancy; test for thiopurine *S*-methyltransferase prior to use is advised	[109, 111, 112]
	MMF	Nephritis, other significant organ involvement	Teratogen; pregnancy must be avoided	[110, 116, 118]
	CYC	Nephritis, cerebritis, myocarditis	i.v. pulses for induction therapy; Euro-Lupus low dose reduces toxicity	[113–115]
Biological	Belimumab	Active disease on standard therapy	Not indicated for nephritis	[122–124]
	Rituximab	Active disease failing other therapies	Trials in nephritis failed endpoints, but use supported by consensus opinion; PML risk	[117, 120, 121]

routine screening of 25-hydroxyvitamin D level is not recommended, and no universal recommendations are available on the screening for vitamin D deficiency in SLE. The desirable 25-hydroxyvitamin D level, set at 30 ng/ml by the Endocrine Society and 20 ng/ml by the Institute of Medicine, remains to be agreed upon [83].

Malignancies

The overall cancer risk for patients with SLE is increased over that of the general population. Recent studies have confirmed previous data showing an increased risk of non-Hodgkin's lymphoma, lung, liver, vulvar/vaginal and thyroid malignancies, and decreased risk of breast and prostate cancer [84]. A role for cell-penetrating anti-DNA antibodies in mediating cancer risk in SLE has been postulated [85]. Recommendations for cancer monitoring in SLE generally follow the regular cancer surveillance programmes already practised in most countries [86].

Medications and other treatment strategies

The heterogeneity of SLE necessitates individualization of treatment strategies. Personalized medicine and treat-to-target are relatively new additions to the medical lexicon that are highly relevant to the care of SLE patients. An international task force has initiated recommendations for a treat-to-target strategy in SLE, with disease remission as the long-term goal [45]. Optimal use of drug interventions requires assessment of risks and benefits in each patient and longitudinal follow-up to determine responses and to make course corrections. The following sections review the evidence for current major drugs and other treatments available for clinical care (Table 1).

HCQ and other antimalarials

The US Food and Drug Administration approved use of HCQ for SLE in 1957, and for many years this was the major drug used for treatment of cutaneous manifestations of SLE. Skin damage may be reduced or delayed by HCQ [87], and treatment of what appears to be a resistant patient should not be abandoned before noncompliance or other causes of rash are ruled out [88, 89]. Discoid lupus is more resistant to HCQ; combination with quinacrine may be more effective than HCQ monotherapy in these patients [90]. One of the few placebo-controlled trials with HCQ documented improvement in joint pain [91]. Surprisingly, this study, carried out >20 years ago, may be the only controlled trial with HCQ that had clinical symptoms as an outcome measure. Even apparently quiescent patients are likely to benefit from continued HCQ, because withdrawal has been shown to be associated with an increased risk of flares [92]. Treatment with HCQ is beneficial for many other aspects of SLE, including haematological abnormalities [93]. Active renal disease requires other immunosuppressive medications, but addition of HCQ to such regimens improves long-term outcomes [94, 95]. Use of HCQ has been correlated with improvement in overall survival [96]. For these and other reasons, such as favourable effects on glucose control [97] and infections [98], the treat-to-target strategy proposes that antimalarial therapy be seriously considered in most SLE patients [45].

Retinal toxicity related to use of HCQ is rare, but regular ophthalmological examinations are required, although the timing and nature of testing varies in different countries. Newer diagnostic tests, such as spectral-domain optical coherence tomography, detect changes early, prior to the classic bull's-eye retinopathy, and with these techniques, retinal abnormalities may be as high as 20% after 20 years of treatment. Risk of HCQ toxicity is minimized by dosing

to a maximum of 5 mg/kg using real, rather than ideal, body weight. Retinal toxicity may be higher in Asians, and with concomitant tamoxifen therapy [99]. Chloroquine carries a higher risk of retinopathy. Quinacrine does not cause retinal damage and might be useful in combination with HCQ [100].

CSs

The use of corticotrophin and cortisone in SLE in the mid-20th century produced the first significant clinical responses in severely ill patients [101]. The adverse effects of CSs were recognized early on, and the general advice was to keep doses as low as possible, which was difficult without availability of any other highly active drugs. In acute situations, such as with onset of GN, cerebritis or myocarditis, high i.v. doses given as pulse therapy of 500–1000 mg methylprednisolone daily for 3–5 days are used to reduce inflammation rapidly and permit other treatments then to take over. Despite the widespread acceptance of this type of therapy, the evidence basis for its use is limited [102, 103]. Lower i.v. doses and oral pulses also may be efficacious; all such decisions still remain empirical. These longstanding practices have been challenged by data indicating that use of CSs is associated with accrual of damage in SLE and that no completely safe level can be identified, leading to the recommendation that control of SLE without the use of CSs should be a long-term goal [45, 104, 105]. Trials to test non-CS protocols formally using MMF or rituximab are ongoing [106].

Immunosuppressants

AZA was introduced into medicine in 1957, and during the 1960s treatment of SLE patients with GN, nephrotic syndrome and CNS disease was shown to be effective and have steroid-sparing effects [107, 108]. Long-term follow-up of patients in the NIH LN trials showed treatment with AZA to be associated with higher renal survival than treatment with glucocorticoids alone [109]. More recently, AZA was shown to be less effective than MMF in maintenance of LN remission [110]. Nevertheless, AZA remains an important part of the SLE pharmacopeia, and it is especially useful for its safety during pregnancy. Testing to be sure that thiopurine *S*-methyltransferase levels are normal prior to initiating treatment with AZA is advised to reduce the risk of significant bone marrow suppression [111, 112].

CYC treatment in SLE was first reported in the 1960s, and the NIH studies subsequently confirmed efficacy in the treatment of LN, leading to widespread use of the monthly i.v. treatment protocol [109]. Risks include infections, such as herpes zoster, and ovarian failure. As an alternative, the Euro-Lupus Nephritis Trial, using a lower-dose regimen, with a cumulative amount of CYC about half that of the standard NIH protocol, was shown to have comparable efficacy [113]. Furthermore, the low-dose protocol was associated with fewer infections and essentially no risk of premature gonadal failure [114]. After 10 years, generally good clinical responses were maintained in the low-dose group, although a decrease in malignancies was not shown [115].

Controlled trials have demonstrated that MMF is an efficacious alternative to CYC for both induction and maintenance phases of SLE renal disease [110, 116]. Guidelines suggest that these two medications are equivalent for the treatment of classes III and IV LN, with preference for using MMF in Hispanic patients [117]. Risks of ovarian failure with MMF are lower than with CYC. Teratogenicity is significant, and counseling about pregnancy avoidance is mandatory [118].

Biologics and off-label therapies

Rituximab, which targets CD20 B cells for deletion, has been used to treat SLE for over a decade. The trials of rituximab in renal and non-renal SLE failed to reach end points, but published guidelines and consensus opinion position rituximab as second- or third-line therapy for renal and CNS forms of SLE [117, 119]. Clinical benefits and safety of rituximab in refractory SLE have been well documented in a large number of non-randomized trials [120]. The combination of rituximab and MMF has been shown to have potential as a CS-free regimen for treatment of LN [121].

Belimumab is a human mAb that binds to B lymphocyte stimulator (also known as B cell activating factor, or BAFF), resulting in diminished B cell lifespan. The US Food and Drug Administration-approved indication for this drug is for adult patients with SLE who have active disease, are autoantibody positive and who are receiving standard therapy with CSs, antimalarials, NSAIDs, MMF and AZA [122]. Belimumab is not presently recommended for use with CYC or in combination with another biological. However, the use of belimumab following rituximab is under investigation, based on the observation that levels of BAFF rise after rituximab treatment [120]. Belimumab has a slow onset of action but is generally well tolerated, with few infectious complications, and may be useful in flaring patients. A recent study demonstrated the presence of BAFF and BAFF receptors in discoid lupus skin lesions, suggesting that this difficult-to-treat condition might be responsive to this targeted biologic therapy [123]. In *post hoc* analyses of the randomized, controlled trials, seropositive SLE patients treated with belimumab showed clinically meaningful improvements in validated measures of health-related quality of life and fatigue compared with placebo-treated control patients [124].

Biologics targeting Type I IFN are currently in trials. Silfalimumab met end points in a placebo-controlled phase IIB trial [125], as did anifrolumab, which blocks all types of type I IFNs and which is now in pivotal phase III trials [126]. Rontalizumab is one that did not meet end points in a phase II trial, but exploratory analyses suggested improvements in some patient subgroups [127]. These emerging data suggest that the therapeutic approach to type I IFN blockade holds promise.

Many other drugs have been used off-label in SLE, including both traditional DMARDs and biologics [128–133] (Table 2).

Table 2 Drugs used off-label for SLE in clinical practice

Conventional DMARDs	Biologics
MTX	TNF inhibitors
LEF	Abatacept
Calcineurin inhibitors	Tocilizumab

Other treatments

Non-pharmacological therapies used to treat SLE include IVIG and plasmapheresis, which are generally reserved for situations where other therapies have failed or when rapid onset of therapeutic effect is needed. Diffuse alveolar haemorrhage associated with SLE is a rapidly progressive condition in which plasmapheresis has shown benefit [134]. IVIG may be efficacious for treatment of cutaneous lupus [135]. All SLE patients should be advised to use sunscreen preparations, which have been shown to decrease inflammation and reduce skin damage.

Summary and conclusions

SLE is a complex disease that impacts persons at relatively young ages, when other chronic conditions are rare. Improved treatments have resulted in many patients living longer, revealing other associated co-morbidities, such as cardiovascular disease and osteoporosis, that require attention. Morbidity and mortality rates have shown steady declines, but remain unacceptably excessive. Advances in understanding the underlying pathogenetic mechanisms are contributing new insights that hold promise for translation into improved clinical care in the future.

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