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REVIEW ARTICLE

Pharmacological Management of Childhood-Onset Systemic Lupus Erythematosus

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Abstract Systemic lupus erythematosus (SLE) is a rare, severe, multisystem autoimmune disorder. Childhood-onset SLE (cSLE) follows a more aggressive course with greater associated morbidity and mortality than adult-onset SLE. Its aetiology is yet to be fully elucidated. It is recognised to be the archetypal systemic autoimmune disease, arising from a complex interaction between the innate and adaptive immune systems. Its complexity is reflected by the fact that there has been only one new drug licensed for use in SLE in the last 50 years. However, biologic agents that specifically target aspects of the immune system are emerging. Immunosuppression remains the cornerstone of medical management, with glucocorticoids still playing a leading role. Treatment choices are led by disease severity. Immunosuppressants, including azathioprine and methotrexate, are used in mild to moderate manifestations. Mycophenolate mofetil is widely used for lupus nephritis. Cyclophosphamide remains the first-line treatment for patients with severe organ disease. No biologic therapies have yet been approved for cSLE, although they are being used increasingly as part of routine care of patients with severe lupus nephritis or with neurological and/or haematological involvement. Drugs influencing B cell survival, including belimumab and rituximab, are currently undergoing clinical trials in cSLE. Hydroxychloroquine is indicated for disease manifestations of all severities and can be used as monotherapy in mild disease. However, the management of cSLE is hampered by the lack of a robust evidence base. To date, it has been principally guided by best-practice guidelines, retrospective case series and adapted adult protocols. In this pharmacological review, we provide an overview of current practice for the management of cSLE, together with recent advances in new therapies, including biologic agents.

Key Points

Robust evidence for the pharmacological management of childhood-onset systemic lupus erythematosus (SLE) is lacking and is principally based on adult data or consensus recommendations.

Immunosuppression is the cornerstone of medical management, consisting of frequent use of glucocorticoids, hydroxychloroquine and steroid-sparing, disease-modifying immunosuppressants; potent therapies are reserved for severe disease.

Specific biologic agents are emerging, including belimumab (the most recently approved drug for adult-onset SLE) and rituximab (already widely used in clinical practice), both of which are currently undergoing clinical trials in childhood-onset SLE.

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1 Introduction

Systemic lupus erythematosus (SLE) is the archetypal systemic autoimmune disease, characterised by autoantibody production against endogenous nuclear autoantigens,

such as antinuclear antibodies (ANAs) and anti-double-stranded DNA (anti-dsDNA). Childhood-onset SLE (cSLE) is a rare condition, with an incidence of 6–30 per 100,000 children per year [1]. This incidence varies with ethnicity, with cSLE being more common in those of Black African or Asian descent, who also have earlier disease onset and more lupus nephritis (LN) [2]. Female preponderance is less pronounced than in adult-onset SLE (aSLE), with a sex ratio of 5:1 as compared with 9:1 [3]. Although the clinical features of cSLE and aSLE are similar, childhood-onset disease is generally more severe, with greater disease activity and damage accrual, lower health-related quality of life scores and overall greater mortality [4–8].

Presentation may typically be with non-specific constitutional symptoms—including fever, lymphadenopathy and weight loss [3]—which may be attributed to a wide range of scenarios such as 'being a teenager', anorexia nervosa or chronic fatigue syndrome. Symptoms may appear intermittently and cumulatively over many months, leading to diagnostic difficulty. Conversely, patients can present with life-threatening acute major organ failure requiring intensive care. Common features include renal, cutaneous and musculoskeletal symptoms, with neurological and haematological manifestations occurring more frequently in childhood-onset disease [4, 9, 10]. Liver, ophthalmic, cardiac and pulmonary involvement are less commonly observed in cSLE [11].

The management of cSLE has been hampered by the lack of a robust evidence base. It has principally been guided by best-practice consensus guidelines, small retrospective case series and adapted adult-derived protocols. Immunosuppression is the cornerstone of medical management, with glucocorticoids still playing an important role. Potent disease-modifying immunosuppressants, such as cyclophosphamide and mycophenolate mofetil, are used for moderate to severe disease, and azathioprine is used for milder disease. Hydroxychloroquine is recommended in all cSLE patients. Biologic therapies have emerged as the next generation of therapeutic options. Despite notable setbacks in their development in aSLE [12], recent successful trials have led to the first drug being licensed for use in aSLE in over 50 years. More trials are currently underway and, more significantly, involve the recruitment of patients with cSLE.

This review presents a summary overview of the pharmacological management of cSLE. It also briefly summarises the underpinning pathophysiology and disease management to contextualise this. Using an electronic data source (the PubMed database), studies including patients with cSLE (aged <18 years) were selected and assessed for their relevance. All study types available in English, excluding those that were single-patient case reports, were included for the purposes of this review. A full systematic review of the literature was beyond the scope of this review. The review summarises the available treatment regimens, as well as emerging biological therapies in both cSLE and aSLE, for their potential application in children.

2 Pathophysiology

SLE is probably not a single condition but, rather, a common end point for a syndrome of numerous pathologies involving a complex interaction between the innate and adaptive immune systems. Its pathogenesis can be summarised by two interacting processes: (1) loss of tolerance of autoantigens and subsequent generation of autoantibodies directed against nuclear antigens; and (2) pathogenic autoantibodies and immune complexes, which result in inflammation and clinical disease manifestation [13]. How and why these processes occur is not yet fully elucidated, but its aetiology is multifactorial, involving environmental, genetic and hormonal factors.

High levels of interferon (IFN)-α were first associated with SLE and disease flares in 1979 [14]. Genetic studies later corroborated these findings, showing increased expression to be associated with greater disease activity [15–17]. cSLE serum contains increased levels of IFN-α, which is pro-apoptotic and leads to increased endogenous nucleic acid (self-antigen) production [18]. IFN-α induces maturation of antigen-presenting cells while simultaneously priming antibody-producing B cells. Autoantigen and autoantibodies then create immune complexes, which are deposited in body tissues, leading to inflammation and a self-perpetuating amplification cycle of further IFN-α production.

There has been considerable scientific attention regarding the genetic susceptibility of lupus patients, and studies have identified, for example, significant upregulation of genes involved in the IFN pathway [15, 16]. To date, approximately 30 associated lupus susceptibility loci have been identified [19].

Toll-like receptors (TLRs)—pattern recognition receptors (PRRs) of the innate immune system—have a critical role in detecting and initiating an immune response against invading pathogens. TLRs 3, 7/9 are important in cSLE because of their unique ability to detect endogenous nuclear antigen [20], which leads to increased type 1 IFN production [21]. Upregulated TLR expression in peripheral blood mononuclear cells (PBMCs) correlates with increased disease activity and anti-dsDNA titres [22]. Defects of the TLR 7/9 signalling pathway are associated with clinical remission [23]. Interleukin-1 receptor-associated kinase 1 (IRAK1)—an adapter protein for the TLR 7/9 pathway—is an SLE-associated gene [24]. A TLR 7/9 inhibitor is currently undergoing phase II

clinical trials in psoriasis. To date, there have been no clinical trials of selective TLR inhibitors in SLE.

T cell profiling in SLE demonstrates an abnormal, pro-inflammatory response rather than a more suppressive, regulatory phenotype [25]. An expansion of T-helper cells in SLE correlates well with increased levels of autoantibodies and disease activity [26]. Dendritic cells (DCs) are the major antigen-presenting cells, bridging the interaction between innate and adaptive immunity. Under normal conditions, apoptotic cells are presented to autoreactive T cells by DCs, leading to inactivation, generating T cell tolerance. However, in SLE, there is an overwhelming quantity of apoptotic material that develops. When this is complexed with autoantibodies, DCs may produce an effective immune response against self-derived nucleic acids, leading to autoimmunity [27]. Abnormal T cell function and cytokine-producing T cells have all been recent targets for drug development in SLE.

Loss of B cell tolerance is a key focus of novel SLE drug discovery research. Antinuclear autoantibodies can be present in SLE patients years prior to the onset of clinical disease, indicating that loss of B cell tolerance occurs early in the disease process [28]. Mechanisms producing B cell tolerance are defective, thus allowing autoreactive B cell clones to expand into the memory compartment. When the disease manifests clinically, there can be absolute B cell lymphopenia but increased levels of immature peripheral blood plasmablasts, correlating positively with autoantibody production and disease activity [29]. B cell–activating factor (BAFF, or B lymphocyte stimulator [BlyS]) is a protein that promotes survival of B cells and has been implicated in the expansion of autoreactive B cells. Serum BAFF levels have also been shown to be increased in SLE [30]. Defective DCs activating autoreactive B cells in SLE stimulate increased production of BAFF, promoting development of more autoreactive B cells, pro-inflammatory cytokines and autoantibody production, within a self-amplifying loop.

3 Diagnosis and Disease Monitoring

Diagnosis of cSLE is at times complicated and requires careful assessment by a multidisciplinary team experienced in the care of paediatric connective tissue disorders. It is informed by a combination of clinical and laboratory findings. The presence of 4 out of 11 of American College of Rheumatology (ACR) classification criteria, either serially or simultaneously, is generally used to make a clinical diagnosis of SLE [31, 32]. The recent Systemic Lupus International Collaborating Clinics (SLICC) classification criteria have been developed to include at least one clinical and one immunological criterion for the classification of SLE, with biopsy-confirmed LN, in the presence of typical SLE autoantibodies, as a stand-alone criterion [33]. This revised system may be more sensitive and specific in cSLE but requires further validation [34, 35].

cSLE classically follows a relapsing–remitting disease course, with unpredictable flares (relapses) followed by periods of disease remission. There is no single reliable laboratory test for early identification or prediction of relapse or remission. The SLE Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) score are composite assessment tools that have been developed to objectively assess and measure overall disease activity [36, 37]. They were originally developed for use in aSLE; both have since been validated for use in cSLE [38]. These tools help differentiate mild to moderate from severe disease activity and help inform treatment choices. SLEDAI and BILAG have both significantly facilitated delivery of clinical trials as objective outcome measures. SLEDAI generates an overall disease activity score but does not specifically discriminate between organ systems, unlike BILAG [39]. Monitoring of the frequency and distribution of irreversible end-organ disease damage is undertaken using the SLICC/ACR Damage Index [40].

4 Management

cSLE requires a multidisciplinary approach in a specialist centre that has experience and expertise in its wide-ranging clinical manifestations. The team should be led by an experienced clinician and should include a paediatric rheumatologist who can co-ordinate the patient's multisystem management, including allied healthcare professionals, according to the individual needs of the patient. This review focuses on pharmacological treatments. However, a holistic approach is required, addressing issues pertinent to a child/young person going through a time of immense physical and psychosocial development.

4.1 Pharmacological Management

The key aim of medical management is to relieve symptoms and improve quality of life by reducing disease activity and preventing permanent tissue damage. Immunosuppression is the focus of pharmacological management, with the intensity of therapy dependent upon the severity of the disease and the distribution of organ involvement. This overview considers pharmacological management of mild to moderate disease contrasted with severe disease. Throughout treatment, the long-term consequences of therapy—for example, steroid-induced side effects, increased risk of infection and future malignancy—

must be balanced against the benefits of disease control through medical management. A list of medication-specific side effects is provided in Table 1.

4.2 Mild to Moderate Disease

Constitutional, mucocutaneous and musculoskeletal features are likely to represent the clinical phenotype in mild to moderate disease. These patients still require systemic treatment and symptom-specific therapies where applicable [41].

4.2.1 Hydroxychloroquine

Hydroxychloroquine (HCQ) is well recognised to offer beneficial effects by improving rheumatic symptoms in patients with SLE [42]. Its positive effect is likely to be due to inhibition of the endosomal TLRs 3, 7/9 [43]. These receptors rely on an acidic environment for optimal binding of their endogenous ligands. Hydroxychloroquine reduces endosomal acidification, inhibiting the binding of potential lupus autoantigen to these TLRs [44], therefore preventing IFN-α production. No trials of hydroxychloroquine have been performed in cSLE. It was effective in lowering the rate of disease flares in a double-blind, placebo-controlled withdrawal study of aSLE patients [45]. When used as an adjuvant to standard LN treatment regimens, hydroxychloroquine is associated with greater renal response and reduced renal relapse rates [46, 47]. It is commonly prescribed at 5–6.5 mg/kg/day (maximum 400 mg) and is recommended at diagnosis for all severities and manifestations of cSLE. It can be used as monotherapy in mild disease, is generally very well tolerated and should be continued over the long term in all patients. Hydroxychloroquine is contraindicated in glucose-6-phosphate dehydrogenase (G6PD) deficiency because of increased risks of thrombocytopenia, agranulocytosis and aplastic anaemia.

4.2.2 Glucocorticoids

Despite the advent of new immunosuppressants, glucocorticoids remain the mainstay of pharmacological management in cSLE, although they have well-recognised adverse effects. They exert their effect on cells of both the innate and adaptive immune systems by reducing cytokine expression, inhibiting access to sites of inflammation and interfering with cell function [48]. Glucocorticoid treatments can ablate the genomic IFN-α signature in SLE, which is important in disease pathogenesis [49]. They are

Table 1 Commonly used medications and their indications and side effects

Medication	Indications	Side effects
Glucocorticoids	Induction and maintenance therapy	Adrenal suppression
	All moderate to severe cases; may be required for mild unremitting disease	Striae
		Obesity
		Changes in mood
		Growth failure
		Osteoporosis
Cyclophosphamide	Induction therapy, usually intravenous	Infertility
	Moderate to severe disease with organ involvement	Hair loss
		Increased risk of infection
		Nausea and vomiting
		Long-term increased risk of malignancy
Mycophenolate mofetil	Induction and maintenance therapy	Abdominal discomfort
	Moderate to severe disease	Diarrhoea
		Liver inflammation
		Increased risk of infection
		Teratogenic in pregnancy
Azathioprine	Maintenance therapy	Increased risk of infection
	Mild, moderate or severe disease	Bone marrow suppression
Methotrexate	Maintenance therapy	Bone marrow suppression
	Musculoskeletal symptoms	Nausea and vomiting
		Liver inflammation
Hydroxychloroquine	All patients	Avoid in pregnancy or G6PD deficiency

G6PD glucose-6-phosphate dehydrogenase

used across the spectrum of disease severity—from topical use to low-dose oral dosing for mild to moderate disease, and high oral dosing and/or intravenous use for those with severe disease. Specific dosing and weaning regimens vary enormously with severity and disease manifestations, and are therefore out of the scope of this review. There have been no controlled clinical trials assessing glucocorticoids in cSLE to date. Therefore, the safest dose, route, frequency and duration of glucocorticoid therapy are unknown. Studies in aSLE have shown glucocorticoids to be an independent cause of irreversible organ damage [50] and an important predictor of morbidity and mortality in SLE [51]. Concerns in a growing child are particularly pertinent, as they can have deleterious effects on body image, bone toxicity and growth potential, and they specifically increase the risks of cataracts and avascular necrosis in comparison with aSLE [4]. The emphasis is on reducing steroid exposure by tapering to the smallest effective dose, alternate-day dosing (where tolerated) and the use of steroid-sparing agents. Published tapering regimens vary enormously (see Table 2 for examples).

4.2.3 Azathioprine

Azathioprine (AZA) is a purine synthesis analogue used as an immunosuppressant in organ transplantation and autoimmune diseases. It is metabolised in the liver to its active component, 6-mercaptopurine (6-MP), and inhibits DNA synthesis through suppression of adenine and guanine synthesis. Its immunosuppressive properties are due to inhibition of cell-mediated immunity via inhibition of T cell growth, resulting in reduced antibody production. It is used as a steroid-sparing medication in cSLE and can be started at 1 mg/kg/day, titrating up to a maximum dose of 3 mg/kg/day, as tolerated. Its benefits include being an oral preparation, once-daily dose frequency and safety in pregnancy. Genetic testing for thiopurine *S*-methyltransferase (TPMT) activity can be carried out prior to initiating therapy, as those with absent activity should not receive azathioprine, and those with reduced activity are at increased risk of myelosuppression, requiring close specialist supervision [52]. There have been no clinical trials assessing the efficacy of azathioprine in cSLE, and guidance is based on data from aSLE trials. It is generally used in the treatment of mild to moderate disease and as a maintenance drug in patients who have received intensive treatment for severe disease manifestations, including mucocutaneous [53] and neuropsychiatric [54] manifestations.

4.2.4 Methotrexate

Methotrexate (MTX) is an antimetabolite drug, which reduces purine and pyrimidine availability in rapidly dividing cells and therefore is used in high doses as a chemotherapeutic agent. In lower doses, it inhibits cell-mediated immunity through inhibition of inflammatory cytokine production. It has immunomodulatory and anti-inflammatory effects, although its precise mechanism of action is unknown. Methotrexate is prescribed weekly as an oral or subcutaneous preparation, starting at 10–15 mg/m^2 and increasing to a maximum of 20 mg/m^2. It improves arthritis, improves mucocutaneous disease and reduces glucocorticoid dose in aSLE [55], but there are only limited and inconclusive data in the paediatric population [56, 57]. It is used in the treatment of musculoskeletal and mucocutaneous phenotypes refractory to hydroxychloroquine and non-steroidal anti-inflammatory drugs in patients not requiring aggressive systemic immunosuppression. Folic acid can be given concurrently to improve its gastrointestinal and oral mucosal adverse effects (see Table 1). Anticipatory nausea and vomiting are the most common adverse effects and often limit its long-term use.

4.3 Severe Disease

Severe disease is determined by the extent of major organ involvement at presentation or at times of disease flares. In children, the most common severe complication is LN [58], followed by neuropsychiatric disease.

4.3.1 Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an oral preparation that inhibits the enzyme inosine monophosphate dehydrogenase, which is required for the proliferation of T and B cells. It is widely used as an immunosuppressive drug in organ transplantation and autoimmune disease. It is most commonly used in LN and is recommended as both induction and ongoing maintenance therapy in three consensus guidelines for LN treatment in cSLE (Childhood Arthritis and Rheumatology Research Alliance [CARRA], European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association [EULAR/ERA-EDTA] and Kidney Disease Improving Global Outcomes [KDIGO]; see Table 2) [58–60]. Recommendations on treatment dose vary (600–1500 mg/m^2/day up to a maximum of 3 g/day). A lower dose of mycophenolate mofetil can be used initially but should be escalated to the target dose within 4 weeks. After 3 months of mycophenolate mofetil treatment, both the EULAR/ERA-EDTA and KDIGO guidelines suggest that if the patient fails to show any improvement or worsens, a change of therapy should be considered. Concomitant corticosteroid treatment regimens vary between the different guidelines and include the option of a

Table 2 Summary of published recommendations for treatment of lupus nephritis (LN) in childhood-onset systemic lupus erythematosus (cSLE)

Protocol	Summary	
CARRA SLE Subcommittee	Glucocorticoids: 1 of 3 glucocorticoid regimens (primarily oral, primarily intravenous, and mixed oral and intravenous)	
	AND	
	Cyclophosphamide: 6 × monthly intravenous cyclophosphamide doses (initial dose 500 mg/m^2, subsequent doses increased not to exceed maximum monthly dose of 1500 mg). Dose should be adjusted for renal insufficiency and a low WBCC nadir	
	OR	
	Mycophenolate mofetil: 600 mg/m^2/dose twice daily with a maximum dose of 1500 mg twice daily. A lower dose could be used at initiation of treatment, but the dose should be escalated to the target dose within 4 weeks of starting therapy	
KDIGO clinical practice guidelines	Class I LN	Treat as dictated by extra-renal clinical manifestations
	Class II LN	Proteinuria >1 g/day: treat as dictated by extra-renal clinical manifestations of lupus
		Proteinuria >3 g/day: treat with glucocorticoids or calcineurin inhibitors
	Class III and IV LN	*Initial therapy*
		Glucocorticoids plus cyclophosphamide or mycophenolate mofetil
		Maintenance therapy
		Azathioprine (1.5–2.5 mg/kg/day) or mycophenolate mofetil (1–2 g/day in divided doses), and low-dose oral glucocorticoids (10 mg/day prednisone equivalent)
	Class V LN	*Normal kidney function and non-nephrotic-range proteinuria*
		Treat as per extra-renal manifestations
		Persistent nephrotic proteinuria
		Glucocorticoids plus cyclophosphamide or mycophenolate mofetil or azathioprine or calcineurin inhibitor
	Class VI LN	Immunosuppressants as dictated by extra-renal manifestations
	Non-responders who have failed >1 recommended initial regime	Consider rituximab, intravenous immunoglobulin or calcineurin inhibitor
EULAR/ERA-EDTA recommendations	Immunosuppressants recommended in class III_A or $III_{A/C}$ (±V) and IV_A or $IV_{A/C}$ (±V) nephritis, and also in pure class V nephritis if proteinuria exceeds 1 g/24 h	
		Initial therapy
	Class III_A or $III_{A/C}$ (±V) and class IV_A or $IV_{A/C}$ (±V) LN	Intravenous methylprednisolone: 3 pulses of 500–750 mg followed by oral prednisolone 0.5 mg/kg/day for 4 weeks, reducing to <10 mg/day by 4–6 months
		Mycophenolate mofetil (3 g/day for 6 months) or cyclophosphamide (cumulative dose: 3 g over 3 months or, in the presence of prognostic factors, 0.75–1 g/m^2 for 6 months or 2–2.5 mg/kg/day for 3 months)
	Class V LN plus nephrotic range proteinuria	Oral prednisolone (0.5 mg/kg/day) plus mycophenolate mofetil (3 g/day for 6 months)
		Alternatives
		Non-responders: cyclophosphamide or calcineurin inhibitor or rituximab
		Patients without adverse prognostic factors: azathioprine (2 mg/kg/day)
		Subsequent treatment—improving
		Prednisolone (5–7.5 mg/day) in combination with mycophenolate mofetil (dose 2 g/day) or azathioprine (2 mg/kg/day) for at least 3 years. Gradual drug withdrawal, glucocorticoids first, can then be attempted

Table 2 continued

Protocol	Summary
Euro-Lupus Nephritis Trial	Glucocorticoids: 3 daily pulses of 750 mg of intravenous methylprednisolone, followed by oral glucocorticoid therapy at an initial dosage of 0.5 mg/kg/day of prednisolone (or equivalent) for 4 weeks. A dosage of 1 mg/kg/day was given in patients with renal impairment or severe extra-renal disease. At 4 weeks, glucocorticoids were tapered by 2.5 mg of prednisolone (or equivalent) every 2 weeks. Low-dose glucocorticoid therapy (5–7.5 mg/day of prednisolone per day) was maintained until at least month 30
	Cyclophosphamide—high dose: the high-dose group received 8 intravenous cyclophosphamide pulses within 1 year (6 × monthly pulses followed by 2 × quarterly pulses). The initial cyclophosphamide dose was 0.5 g/m^2; subsequent doses were increased by 250 mg according to the WBCC nadir measured on day 14, with a maximum of 1500 mg per pulse
	Cyclophosphamide—low dose: fortnightly intravenous cyclophosphamide pulses at a fixed dose of 500 mg
	Azathioprine: 2 mg/kg/day was started 2 weeks after the last cyclophosphamide injection and continued until at least until month 30

CARRA Childhood Arthritis and Rheumatology Research Alliance, *EULAR/ERA-EDTA* European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association, *KDIGO* Kidney Disease Improving Global Outcomes, *LN* lupus nephritis, *WBCC* white blood cell count

mycophenolate mofetil and glucocorticoid oral-only induction regimen (see more detail in Table 2).

To date, there has been one randomized, controlled trial (RCT) of mycophenolate mofetil involving children. The Aspreva Lupus Management Study (ALMS) Group carried out a phase III clinical trial comparing the efficacy of mycophenolate mofetil as induction and maintenance therapy in LN [61]. The study had 370 participants, including 24 adolescent patients between the ages of 12 and 18 years. Because of the small number of patients, the authors conceded that the study was insufficiently powered to detect a statistically significant difference. The induction phase of the study was an open-label comparison of oral mycophenolate mofetil and intravenous cyclophosphamide, and it failed to demonstrate a difference between the two therapies. Sixteen patients were enrolled into the maintenance phase, which was a double-blind comparison of prednisolone plus azathioprine or mycophenolate mofetil. This showed a trend towards greater efficacy of MMF as a maintenance therapy but, again, failed to reach significance. Interestingly, MMF showed highly statistically significant superiority to azathioprine in the adult group; however, this finding has yet to be validated in the paediatric population.

Other than this one underpowered RCT, the evidence is limited to a non-controlled cSLE study, which demonstrated mycophenolate mofetil to be effective in improving renal function in patients with membranous glomerulonephritis but not proliferative glomerulonephritis, improving disease activity and facilitating steroid tapering in both types of nephritis [62]. A retrospective case series of nine children with SLE, assessing mycophenolate mofetil as maintenance therapy for LN, demonstrated reduced disease activity and a glucocorticoid-sparing effect [63]. Adult studies have shown mycophenolate mofetil to be effective in treating LN (III/IV), with a favourable adverse effect profile, including fertility [39].

4.3.2 Cyclophosphamide

Cyclophosphamide (CYC) is metabolised to 4-hydroxy-cyclophosphamide and is a potent broad-spectrum immunosuppressant with a significant adverse effect profile. It is therefore reserved for patients with severe major organ involvement where rapid disease control is required. Its beneficial effect in SLE is due to its ability to modulate the T cell response and B cell antibody production. It was developed over 60 years ago and thus has one of the strongest evidence bases for use in cSLE, where trials have shown that it is effective in inducing remission in severe LN in children [39, 57, 64–66]. Its use is recommended in cSLE LN consensus guidelines (see Table 2) [58–60] as an alternative option to mycophenolate mofetil. Again, the recommendations vary, with a suggested duration of initial therapy of 3–6 months and a dosage varying from 500 to 1500 mg/m^2 or a cumulative dose of 0.75–3 g/m^2 dependent on the duration of therapy and the presence of prognostic factors. A European trial assessing the efficacy of high-dose (six pulses of 500–1500 mg/m^2) versus low-dose (six pulses of 500 mg/m^2) cyclophosphamide regimens in aSLE found that the low-dose regimen followed by azathioprine was as efficacious as the high-dose regimen [67].

Table 1 highlights the adverse effects of cyclophosphamide, the most concerning of which is the risk of long-term infertility. Premature gonadal failure is a concern especially for females commencing on cyclophosphamide and can lead to apprehension in consenting to therapy. Meticulous monitoring of the cumulative dose

administered is required to mitigate this risk. Prepubertal girls are relatively protected from this effect, with the risk in girls under 25 years of age being approximately 11 %, increasing to over 40 % above this age [68]. Traditional methods to preserve fertility in adults involve the harvesting of oocytes; however, this is ethically controversial in children. Gonadotropin-releasing hormone (GnRH) agonists reduce the incidence of ovarian failure in women with aSLE undergoing cyclophosphamide therapy [69]. This effect is thought to arise through inhibition of the pituitary–gonadal axis, decreasing oocyte maturation and causing the germinal epithelium to be less susceptible to gonadotoxic insults. Triptorelin, a GnRH agonist, has undergone a phase II clinical trial in cSLE, which showed it to be safe and able to completely suppress ovarian function [70]. Further trials to assess its efficacy are required; however, if they are positive, it may prove to be an important option. In pubertal boys, sperm banking is a realistic option but must be handled in a delicate manner.

4.3.3 Rituximab

Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody (mAb) originally developed for the treatment of B-cell lymphomas. It induces apoptosis upon binding of the CD20 cell surface antigen expressed selectively on B cells—including immature, naïve and memory B cells—but not on pro-B cells, early pre-B cells or plasma cells; therefore, its potential role for therapeutic benefit is clear. It was initially approved for the treatment of non-Hodgkin's lymphoma and has since been successfully tested in RCTs in many autoimmune disorders, including rheumatoid arthritis [71, 72]. B cell depletion therapy was subsequently shown to be effective in mouse models of SLE [73]. The Exploratory Phase II/III SLE Evaluation of Rituximab (EXPLORER) trial was designed to assess the beneficial effect of rituximab on the induction and maintenance of clinical response in adults with non-renal SLE. Notably, it failed to meet both its primary and secondary outcome measures [74]. The Lupus Nephritis Assessment With Rituximab (LUNAR) trial investigated rituximab versus placebo in addition to standard care (mycophenolate mofetil and glucocorticoids) in adult patients with LN [75]. This trial also failed to meet any primary or secondary outcome measures. In both trials, post hoc analysis showed a beneficial effect of rituximab in specific subgroups. There are a number of reasons why these trials may have failed: concomitant therapy was used, which may have masked a treatment effect; previous regimens of rituximab also used cyclophosphamide, which could have had a synergistic effect, while these trials used mycophenolate mofetil; and the study duration may not have been optimal, with a median time to renal response of 1–2 years [67, 76, 77].

Rituximab is the most frequently used biologic in cSLE despite robust evidence for its effectiveness being limited. It has typically been reserved for either severe, intractable disease; cases that have failed other therapies; or those patients experiencing unwanted adverse effects from alternative treatments—and it has been recommended for this scenario by the KDIGO clinical practice guidelines for LN (see Table 2) [59]. A retrospective analysis of 63 patients from the UK Juvenile-Onset Systemic Lupus Erythematosus (JSLE) cohort study over 10 years showed that rituximab reduced disease activity and the steroid burden when used in those patients failing standard care, with a relatively good safety profile [78]. This was echoed by a case series of 12 patients, which showed benefit for up to 5 years [66]. Two other studies in cSLE have also demonstrated benefit in patients with severe disease who have failed standard therapy [79, 80], and rituximab is increasingly being considered as part of routine management of severe disease.

The ongoing Trial of Rituximab and Mycophenolate Mofetil Without Oral Steroids for Lupus Nephritis (RITUXILUP) trial (ClinicalTrials.gov study ID NCT01773616) is an open-label, multicentre RCT with the aim of demonstrating the efficacy of rituximab with mycophenolate mofetil versus mycophenolate mofetil and glucocorticoids only in LN. It will also assess this regimen's steroid-sparing potential. Significantly, this trial includes a cSLE cohort (children aged >12 years) and will help inform future management where the effects of LN and the steroid burden are most significant. The Rituximab for Lupus Nephritis With Remission as a Goal (RING) trial (ClinicalTrials.gov study ID NCT01673295) is another phase III trial that will also examine rituximab in refractory LN and will include patients aged ≥15 years.

4.3.4 Belimumab

BAFF (or B lymphocyte stimulator [BlyS]) and a proliferation-inducing ligand (APRIL) are members of the tumour necrosis factor (TNF) ligand superfamily [81]. BAFF is present in soluble and membrane-bound forms and binds to three B cell receptors: BAFF receptor (BAFF-R), B cell maturation antigen (BCMA) and transmembrane activator and CAML [calcium-modulating ligand] interactor (TACI). It is vital for B cell survival and plays an important role in B cell maturation, immunoglobulin production and class switching [81]. APRIL is structurally similar to BAFF, is capable of binding to BCMA and TACI, and has similar effects to BAFF [82]. Overexpression of BAFF in mouse models leads to the development of SLE-like autoimmune features, with BAFF and APRIL inhibition showing therapeutic benefit [83, 84]. BAFF levels are elevated in SLE, correlating with disease activity

[85]. These findings have led to the development of this class of drugs in SLE.

Belimumab is a fully humanized mAb that binds soluble BAFF and prevents it from binding with its receptors. Two phase III clinical trials in aSLE—the Study of Belimumab in Subjects With Systemic Lupus Erythematosus (BLISS)-52 and BLISS-76—assessed belimumab alongside standard SLE therapy and demonstrated a significant response with low-dose and high-dose treatment as compared with placebo, together with a favourable side-effect profile [86–88]. The duration of response was more sustained, the steroid dose could be tapered and the rates of severe flare were reduced in comparison with placebo at week 52 of follow-up [87, 88]. Greater therapeutic benefit was found in patients with autoantibody-positive disease, greater disease activity, low complement and corticosteroid use at baseline. These findings led to US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval of belimumab in autoantibody-positive aSLE, with the National Institute for Health and Care Excellence (NICE) due to make a decision soon in the UK. However, there are aspects of belimumab treatment that require further investigation. In BLISS-76, the positive effects of treatment were not sustained at 76 weeks, and patients with central nervous system disease or severe LN were not recruited [86, 87].

Belimumab is currently undergoing the phase II, randomized, double-blind Pediatric Lupus Trial of Belimumab Plus Background Standard Therapy (PLUTO) trial (ClinicalTrials.gov study ID NCT01649765) to assess its pharmacokinetics, safety and efficacy in 5- to 17-year-old patients who have active, autoantibody-positive cSLE. The primary outcome measures are expected to be available in late 2016. It is encouraging that this drug will be given the opportunity to demonstrate its benefits in children under trial conditions.

4.4 Emerging Biologic Therapies in Adult-Onset SLE

Biologic agents are designed to specifically target aspects of the immune system. Figure 1 illustrates the mechanisms of action of emerging biologics in relation to SLE pathogenesis. Clinical trials involving ten other biologics have been conducted or are ongoing in aSLE (see Table 3). Without legislation to ensure that the planned development of new biologics include children, the lack of studies including or specific to children would continue the current situation in which treatment in children is based principally on data derived from adult clinical trials. Medicines with potential benefit to children should be trialled in children, ideally in conjunction with adult clinical trials.

4.5 Other Disease Consequences

4.5.1 Bone Health

Children with cSLE often fail to acquire peak bone mass and have osteopenia more commonly than healthy children, with an increased risk of developing osteoporosis as adults [89]. The reasons for this include the effect of a chronic inflammatory disorder and medication side effects. Steroids have been shown to be an independent risk factor for low bone mineral density (BMD), and an increased cumulative dose demonstrates an inverse correlation with BMD [90]. Therefore, the emphasis is on prevention. The lowest effective dose of steroids should be used for the shortest possible duration and supplemented by steroid-sparing agents where possible. Bisphosphonates are recommended for use in aSLE, but there is currently no recommendation in children [91].

Denosumab is a human mAb that inhibits the receptor activator of the nuclear factor kappa-B ligand (RANKL) signalling pathway, which has been shown to be a key driver of bone destruction in rheumatic disease [92]. It has been trialled across a wide range of conditions, including rheumatic disorders, and has a UK licence for prevention of osteoporotic fractures in postmenopausal women and skeletal-related events in adults with bone metastases from solid tumours [93]. Trials in rheumatoid arthritis have shown it to increase BMD and reduce progression of bone erosions [94, 95]. A phase I/II, randomized, open-label trial (ClinicalTrials.gov study ID NCT02418273) will assess its efficacy in preventing bone loss in children with rheumatic diseases, including cSLE.

5 Challenges Facing Management of Childhood-Onset SLE

Despite the abundance of clinical trials being conducted with biologics in aSLE, only a minority have been undertaken to date in cSLE. This is despite the fact that early remission can provide greater benefit in prospective years, which is particularly important in lifelong conditions commencing in childhood. The development of drugs for rare diseases poses logistical, economic and ethical challenges. Pharmaceutical agents are unlikely to be trialled in children until adult efficacy has been proven, often delaying potentially effective drugs reaching paediatric patients. The result of this is that over half of the medicines for children have not been adequately studied for their purpose; therefore, their use is unlicensed [96]. The US FDA paediatric exclusivity program was passed in 1997 and provided financial incentives for drugs studied in paediatric populations, with the aim of increasing research and drug

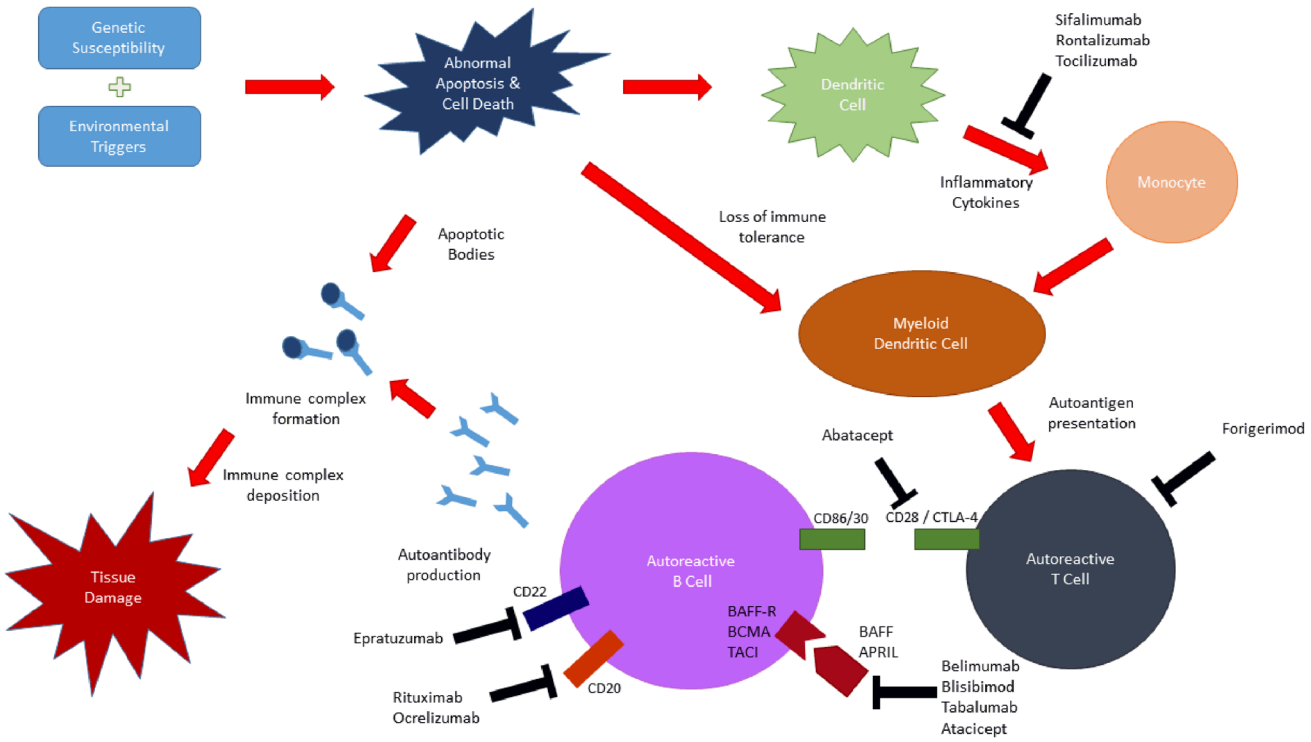

Fig. 1 Pathogenesis and biologic therapy in systemic lupus erythematosus (SLE). The use of biologics in SLE employs four main strategies: targeting of B cells, interruption of B–T cell co-stimulation, targeting of T cells and anti-cytokine therapy. Although these therapies act at different points of the immune system, their common aim is inhibition of an autoimmune response. *APRIL* a proliferation-inducing ligand, *BAFF* B cell–activating factor, *BAFF-R* BAFF receptor, *BCMA* B cell maturation antigen, *CTLA* cytotoxic T-lymphocyte-associated protein, *TACI* transmembrane activator and CAML [calcium-modulating ligand] interactor

development for children. The European Union (EU) Paediatric Drug Regulation (PDR) was instituted a decade later and also provided financial incentives for paediatric research and drug development. To date, the number of new paediatric indications triggered by the EU PDR has not increased significantly [97]. However, many trials are due for completion in the next few years, and the full benefit of this scheme for children and young people will become clearer.

Clinical trials in SLE have been notoriously difficult to conduct, with several promising drugs failing either because of trial design or inability to produce the expected benefits [98, 99]. Noted issues with trial design have been identifying the correct population for the intended intervention and the importance of achieving statistical power [100]. Successful trials have employed a very large numbers of patients and a flexible design [100]. Achieving success in cSLE clinical trials may therefore prove difficult, where recruiting large study numbers from a relatively small pool of patients can be challenging. To overcome this issue, novel trial designs may be required [101]. The complexities of pathogenesis are vast, and resources are limited, but it is only when this disease process is more fully understood that therapeutic advances will be made.

6 Summary

cSLE is a severe, heterogeneous, multisystem autoimmune condition, which arises through a complex interplay between genetic, environmental and hormonal factors. Its management involves the use of immunosuppressants of varying potencies. Recent scientific advances have improved our understanding of the complex pathogenesis of SLE and provided insight into novel therapeutic targets. A series of biological agents that have been developed to target the immune system have had a significant impact on the management of other autoimmune disorders. As yet, there has been a limited impact on their contribution to the treatment of aSLE and/or cSLE. Challenges faced in developing drugs for cSLE include a small study population and historical difficulties in conducting clinical trials within children and SLE as a whole. Further well-designed

Table 3 Summary of biologic trials in adult-onset systemic lupus erythematosus (aSLE)

Target	Drug	Molecule	RCT phase[a]	Summary of evidence
B cell	Blisibimod	Anti-BAFF peptibody	III (CHABLIS-SC1)	PEARL-SC (phase IIb) study found blisibimod to be effective versus placebo [102]
	Tabalumab	Humanized anti-BAFF mAb	III (NCT01205438; NCT01196091; NCT01488708)	Efficacy was demonstrated in biologic-naïve rheumatoid arthritis patients, but no benefit was shown in patients who had previously failed anti-TNF therapy [103, 104]
	Atacicept	Anti-BAFF and APRIL human fusion protein	Discontinued	2 phase II/III trials were discontinued prematurely because of serious adverse events, including two fatalities [105, 106]
	Epratuzumab	Humanized anti-CD22 mAb	III (NCT01261793; NCT01262365)	2 RCTs in patients with moderate to severe disease showed improvement versus placebo but were discontinued early because of an interruption in drug supply [107]. A phase IIb trial showed a non-significant benefit [108]
	Ocrelizumab	Humanized anti-CD20 mAb	Discontinued	Phase III trial was discontinued early because of an increased rate of serious infections [109]
B–T cell co-stimulation	Abatacept	CTLA-4 and immunoglobulin fusion protein	II (NCT02270957)	Phase IIb trial in non-renal lupus and LN failed to meet primary end points. Post hoc analysis suggested a benefit in flare reduction, particularly in patients with polyarthritis [110]
T cell	Forigerimod	21-mer peptide	III	2 phase II trials demonstrated safety and therapeutic efficacy [111, 112]
Cytokines	Sifalimumab	Humanized anti-IFN-α mAb	II (NCT01031836)	Reduced IFN signature but non-significant response versus placebo [113]
	Rontalizumab	Humanized anti-IFN-α mAb	Discontinued	Reduced IFN signature but non-significant response versus placebo [114, 115]
	Tocilizumab	Humanized immunoglobulin G1 anti-IL6R mAb	No present RCT	Phase I trial demonstrated a significantly reduction disease activity; however, there was a dose-related decline in the neutrophil count. Further testing is required to ascertain optimal dosing [116]

APRIL a proliferation-inducing ligand, *BAFF* B cell–activating factor, *CHABLIS-SC1* Study of the Efficacy and Safety of Subcutaneous Blisibimod in Subjects With Systemic Lupus Erythematosus, *CTLA* cytotoxic T-lymphocyte-associated protein, *IFN* interferon, *IL6R* interleukin-6 receptor, *LN* lupus nephritis, *mAb* monoclonal antibody, *PEARL-SC* Study of the Efficacy, Safety, and Tolerability of A 623 Administration in Subjects With Systemic Lupus Erythematosus, *RCT* randomized, controlled trial, *TNF* tumour necrosis factor

[a] The NCT numbers are ClinicalTrials.gov study IDs

trials of appropriate agents are required in children to inform and improve future management.

Compliance with Ethical Standards

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