**­­­­­PEDIATRIC DRUGS**

**Title:** Pharmacological management of childhood-onset systemic lupus erythematosus: a review

**Authors**

Dr Colin Thorbinson, MBChB MRCPCH MPhil is NIHR Academic Clinical Fellow at the University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Dr Louise Oni, MBChB MRCPCH MA PhD is NIHR Academic Clinical Lecturer at the University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Dr Eve Smith, MBChB MRCPCH is a Clinical Research Fellow at the University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Dr Angela Midgley, PhD is a Research Associate at the University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

Professor Michael W Beresford, MBChB MRCP (UK) MCRPCH PhD is Professor of Child Health and Honorary Consultant Paediatric Rheumatologist at the University of Liverpool, Alder Hey Children's NHS Foundation Trust, Liverpool, UK

**Corresponding Author:**

Professor Michael W. Beresford

Department of Women’s and Children’s Health

Institute of Translational Medicine (Child health)

Alder Hey Children’s NHS Foundation Trust Hospital

Eaton Road

Liverpool

L12 2AP

m.w.beresford@liverpool.ac.uk

+44 151 252 5693

**ABSTRACT**

Systemic lupus erythematosus (SLE) is a rare, severe, multisystemic autoimmune condition. 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 but it is recognised to be the archetypal autoimmune disease arising due to 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-moderate manifestations. Mycophenolate mofetil and cyclophosphamide are reserved for those with severe disease manifestations. No biologic therapies are yet to be approved for cSLE however drugs influencing B cell survival, Belimumab, recently approved for aSLE, and Rituximab, recommended for treatment of paediatric lupus nephritis, are currently undergoing clinical trials in cSLE. Adjuvant medications, such as hydroxychloroquine are indicated for disease manifestations of all severities and can be used as monotherapy in mild disease. The management of cSLE is hampered by the lack of a robust evidence base and it is therefore principally guided by best practice guidelines, small retrospective case series and adapted adult protocols. In this pharmacological review, we will cover recommended 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 cSLE is lacking and based on adult data or consensus recommendations.
* Immunosuppression is the cornerstone of medical management with frequent use of glucocorticoids; adjuvant therapies such as hydroxychloroquine; steroid sparing immunosuppressants; and potent therapies reserved for severe disease.
* Specific biologic agents are emerging within the treatment armoury. Belimumab, the most recent drug to be approved for aSLE, and Rituximab are currently undergoing clinical trial in cSLE and will hopefully set a precedent for new therapies to be evaluated.

1. **INTRODUCTION**

Systemic Lupus Erythematosus (SLE) is the archetypal systemic autoimmune disease characterised by autoantibody production against endogenous nuclear autoantigen, such as antinuclear antibodies (ANA) and anti-double stranded DNA (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 gender ratio of 5:1 as compared to 9:1 [3]. Although clinical features of cSLE and aSLE are similar, paediatric disease is more severe, with greater disease activity, damage accrual, lower health related quality of life scores and an overall greater mortality [4-10].

Presentation may typically be with non-specific constitutional symptoms, such as fever, lymphadenopathy and weight loss [3] that may be attributed to ‘being a teenager’, anorexia nervosa, or chronic fatigue syndrome. Symptoms may appear intermittently and cumulatively over many months rather than in parallel, 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 abnormalities; with neurological and haematological manifestations occurring more frequently in childhood-onset disease [4, 11-14]. Liver, ophthalmic, cardiac and pulmonary involvement are less commonly observed in cSLE [15].

Historically the management of cSLE has been hampered by the lack of a robust evidence base and principally been guided by best practice consensus guidelines, small retrospective case series and adapted adult protocols. Immunosuppression is the cornerstone of medical management with glucocorticoids still playing a leading role, as well as potent disease-modifying immunosuppressants such as cyclophosphamide (CYC) and mycophenolate mofetil (MMF) for moderate-severe disease and azathioprine (AZA) for milder disease. Hydroxychloroquine (HCQ) is as an adjuvant therapy which is recommended in the majority of cSLE patients. Biologic therapies are the next generation of medical management and have successfully been introduced in other rheumatological conditions. Their development has had several notable setbacks in SLE [16], however 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 article aims to present an overview of the pathogenesis of cSLE that provides the foundation needed to understand its pharmacological management, which is the specific focus of this review. Using electronic data sources (Pubmed database), studies including patients with cSLE (children were defined as being aged <18 years) involving the drug in question were selected and scrutinized 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. Using these methods, treatment regimens of established SLE therapeutics/drugs will be covered as well as emerging biological therapies in both cSLE and aSLE due to their potential application in children.

1. **PATHOPHYSIOLOGY**

It is a widely held belief that SLE is 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 system. Its pathogenesis can be split into two distinct yet interacting processes: (1) loss of tolerance to self-antigen and generation of auto-antibodies; (2) pathogenic auto-antibodies and immune complexes which result in inflammation and clinical disease manifestation [17]. How and why this occurs has yet to be elucidated, but evidence has shown its aetiology is likely to be multifactorial involving environmental, genetic and hormonal factors. These underlying factors require further exploration to identify new therapeutic targets and develop more effective treatments.

**IFN-α**

High levels of IFN-α were first associated with SLE and disease flares in 1979 [18]. Gene studies have later corroborated these findings, showing increased expression to be associated with greater disease activity [19-23]. Correspondingly IFN-α up-regulation is found in greater than 90% of cSLE patients compared to 70-80% of those with adult-onset disease [23]. There are several proposed theories on the role of IFNs in the pathogenesis of SLE. SLE serum contains increased levels of IFN-α that has been shown to be pro-apoptotic which potentially leads to the release of endogenous nucleic acids (self-antigen)[24]. It also has the ability to induce the maturation of antigen presenting cells while simultaneously priming antibody producing B cells. Auto-antigen and auto-antibodies then create immune complexes which deposit in body tissues, for example in the kidney, leading to inflammation and a self-perpetuating, amplification cycle of further IFN-α production.

**Genetics**

There is a clear genetic link directly contributing to certain SLE phenotypes in an important minority of patients, however the majority of cases of SLE are thought to arise on a background of susceptibility involving multiple genes. The first genetic studies focusing on SLE were conducted in the early 2000’s and identified significant upregulation of genes involved in the IFN pathway [19, 20, 23]. This has been further confirmed using a modular transcriptional approach in which IFN-associated modules were strongly upregulated in cSLE [21, 22]. To date this technique has been used to identify approximately 30 robustly associated lupus susceptibility loci across several populations [25]. However despite these advances none have yet directly contributed to a treatment breakthrough.

**TLRs**

Toll-like receptors (TLRs) are pattern recognition receptors (PRR) of the innate immune system. They have a critical role in detecting and initiating an immune response against invading pathogens [26]. TLRs 3,7-9 have received attention in cSLE due to their unique ability to detect endogenous nuclear antigen [27] the process of which leads to the production of type 1 interferon [28]. They have been shown to be up-regulated in peripheral blood mononuclear cells (PBMCs) and this up-regulation correlates well with disease activity and anti-dsDNA titres [29-31]. Defects of the TLR 7/9 signalling pathway have been associated with clinical remission, further supporting their role in SLE pathogenesis [32, 33]. Interleukin-1 receptor-associated kinase 1 (IRAK1), an adapter protein for the TLR 7/9 pathway, has also been identified as an SLE associated gene [34]. A TLR 7-9 inhibitor is currently undergoing phase 2 clinical trial in psoriasis, however this class of drug still undergoing evaluation in lupus animal models, and no clinical trials in SLE have been carried out to date.

**T Cells**

Recent evidence has suggested an abnormal T cell profile in SLE representing a more pro-inflammatory role as compared to its usual suppressive regulatory character [35]. Expansion of T-helper cells correlate well with increased levels of auto-antibodies and disease activity, supporting this theory [36, 37]. Dendritic cells (DCs) are the major antigen presenting cell in the body, bridge the gap between innate and adaptive immunity and are the main source of nucleic acid containing, immune complex induced IFN-α. Under normal conditions apoptotic cells are presented to auto-reactive T cells by DCs in a fashion that leads to their inactivation, generating T cell tolerance. However there is evidence that when there is an overwhelming volume of apoptotic material, as suggested to occur in SLE, and/or when this is complexed with autoantibodies, DCs may incorrectly produce an effective immune response against self-derived nucleic acids leading to autoimmunity [38]. Given this, B-T cell communication, abnormal T cell function and cytokine producing T cells have all been recent targets for drug development in SLE.

**B Cells**

As SLE is characterised by autoantibody production, loss of B cell tolerance has become a key focus in novel SLE drug discovery research. Anti-nuclear 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 [39]. Mechanisms producing B cell tolerance are defective thus allowing autoreactive B cell clones to expand into the memory compartment [40]. 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 [41]. 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 [42]. In part, SLE pathogenesis is thought to involve defective DC’s activating autoreactive B cells, stimulating the increased production of BAFF which promotes the development of more autoreactive B cells, pro-inflammatory cytokines and autoantibody production, within a self-amplifying loop.

**3. DIAGNOSIS & DISEASE MONITORING**

Diagnosis of cSLE is based on a combination of clinical and laboratory findings, and the American College of Rheumatology (ACR) classification criteria of SLE assists with the diagnostic process [43, 44]. Generally, four out of eleven criteria, present serially or simultaneously, are required for a clinical diagnosis of SLE. The SLICC (Systemic Lupus International Collaborating Clinics) classification criteria have been developed to include at least one clinical and one immunologic criterion for the classification of SLE, with biopsy confirmed LN, in the presence of typical SLE auto-antibodies, as a stand-alone criterion [45]. This revised system appears to be more sensitive and specific in cSLE, but requires further validation [46, 47]. A few patients may never meet all of the classification criteria but there may still be a strong clinical suspicion of SLE, or alternatively may display features of more than one classical autoimmune disease and be described as having an ‘overlap’ or ‘undifferentiated’ connective tissue disease.

SLE 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 the early identification or prediction of relapse or remission [48]. 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 [49, 50]. They were originally developed for use in aSLE, subsequently both have been validated for use in cSLE [51]. These tools have the ability to differentiate mild and moderate from severe disease activity. In doing this they have a role in informing treatment choices. Both SLEDAI and BILAG have similar roles and have significantly facilitated the progress of clinical trial as objective outcome measures. SLEDAI generates an overall disease activity score, therefore it does not specifically discriminate between organ systems unlike BILAG [52].

Monitoring of the frequency and distribution of irreversible end organ disease damage is undertaken using the SLICC / ACR damage index [53].

**4. MANAGEMENT**

cSLE requires a multi-disciplinary approach in a specialist centre that has experience and expertise in its wide ranging clinical manifestations. The team should be led by a paediatric rheumatologist who can co-ordinate the different medical specialities, alongside allied healthcare professionals according to the needs of the individual. Whilst management is almost universally centred on pharmacological treatments, a holistic approach is required addressing issues pertinent to a child / young person going through a time of immense physical and psychosocial development.

**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 distribution of organ involvement. 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.

**MILD-MODERATE DISEASE**

Constitutional, mucocutaneous and musculoskeletal features are likely to represent the clinical phenotype in mild-moderate disease, often termed non-major organ involvement. These patients still require systemic treatment, and symptom specific therapies where applicable [54].

***Hydroxychloroquine***

Hydroxychloroquine (HCQ) is an anti-malarial drug which has been shown to be beneficial in improving rheumatic symptoms in patients with rheumatoid arthritis and SLE [55]. Its positive effect is thought to be due to the inhibition of the endosomal TLRs 3, 7-9 [56]. These receptors rely on an acidic environment for the optimal binding of their endogenous ligands. HCQ reduces endosomal acidification inhibiting the binding of potential lupus autoantigen to these TLRs [57], therefore preventing IFN-α production. No trials of HCQ have been performed in cSLE however it has been shown to be effective in lowering the rate of disease flares in a double-blinded, placebo controlled withdrawal study in 47 patients with aSLE [58]. When used as an adjuvant to standard lupus nephritis treatment regimens, HCQ has been associated with greater renal response and reduced renal relapse rates [59, 60]. It is given at 5-6.5mg/kg/day (max 400mg) and is recommended at diagnosis for all severities and manifestations. It can be given as monotherapy in mild disease, is generally very well tolerated and should be continued over the long-term for all patients. Of note, HCQ is contraindicated in G6PD deficiency due to increased risk of thrombocytopaenia, agranulocytosis and aplastic anaemia.

***Glucocorticoids***

Disappointingly, despite the development of new immunosuppressants, glucocorticoids are still the mainstay of pharmacological management in SLE, despite their well-recognised adverse effects. They exert their effect on cells of both the innate and adaptive immune system by reducing cytokine expression, inhibiting access sites of inflammation and interfering with cell function [61]. In SLE glucocorticoid treatment can ablate the genomic IFN-α signature, thought to be important in disease pathogenesis [23]. They are cheap, clinically effective and have application across the spectrum of disease severity from topical use / low oral dosing for mild-moderate disease, to high oral dosing (Prednisolone) / intravenous use (Methylprednisolone), for those with severe disease. There have been no clinical studies assessing glucocorticoids in cSLE to date, therefore the safest dose, route, frequency and duration of glucocorticoid therapy is unknown. Studies in aSLE have shown glucocorticoids to be an independent cause of irreversible organ damage [62], and an important predictor of morbidity and mortality in SLE [63]. Concerns in a growing child are particularly pertinent as they can have deleterious effect on body image, bone toxicity, growth potential, and specifically increase the risk of cataracts and avascular necrosis as compared to aSLE [4]. This is acknowledged in recommendations for cSLE as compared to aSLE, for example in LN, where guidelines are identical with the caveat that consideration should be given to the negative effect of disease activity and glucocorticoids on linear growth and body image. Therefore 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.

***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 although its mechanism of action has not been fully elucidated it is thought to inhibit DNA synthesis through the suppression of adenine and guanine synthesis. Its immunosuppressive properties are thought to be due to the inhibition of cell mediated immunity via the inhibition of T cell growth which also results in reduced antibody production. It is used as a steroid-sparing medication in cSLE and can be started at 1mg/kg/day titrating up to a maximum dose of 3mg/kg/day, as tolerated, and is usually continued for at least 12 months prior to change of therapy. Its benefits include being an oral preparation, once daily dose frequency and safety in pregnancy. Genetic testing for TPMT activity should be carried out prior to initiating, as those with absent activity should not receive AZA, and those with reduced activity are at increased risk of myelosuppression requiring close specialist supervision. There have been no clinical trials assessing its efficacy in cSLE and treatment is based on data from aSLE trials. It is an adjuvant medication and can be used in the treatment of mild-moderate disease and as a maintenance drug in patients who have received intensive treatment for severe disease manifestations, with specific recommendations for mucocutaneous [64] and neuropsychiatric [65] manifestations.

***Methotrexate***

Methotrexate (MTX) is an antimetabolite drug that reduces the purine and pyrimidine availability in rapidly dividing cells and therefore in high doses is used as a chemotherapeutic agent. In lower doses it is thought to inhibit cell mediated immunity through inhibition of inflammatory cytokine production and therefore has an immunomodulatory and anti-inflammatory effect, however this mechanism of action is unknown. MTX is prescribed weekly as an oral or subcutaneous preparation starting at 10-15mg/m2 increasing to a maximum of 25mg/m2. It has been shown to improve arthritis and mucocutaneous disease and reduce glucocorticoid dose in aSLE [66], with limited and inconclusive results in the paediatric population [67-69]. It is suitable for the treatment of musculoskeletal and mucocutaneous phenotypes refractory to HCQ and non-steroidal anti-inflammatory drugs in those 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.

**SEVERE DISEASE**

Severe disease is determined by the extent of major organ involvement at presentation or times of disease flares. In children, the most common severe complication is LN [70], followed by neuropsychiatric disease. Other severe manifestations include, cardiac and pulmonary, however these occur relatively infrequently in cSLE as compared to aSLE.

***Mycophenolate Mofetil***

Mycophenolate Mofetil (MMF) is an oral preparation which inhibits the enzyme inosine monophosphate dehydrogenase required for the proliferation of T and B cells and is widely used as an immunosuppressive drug in organ transplantation and autoimmune disease. It is primarily used in SLE is as an induction agent and maintenance treatment of severe systemic manifestations. It is most commonly used in LN and is recommended as both an induction and as on-going maintenance therapy in three consensus guidelines for LN treatment in cSLE (CARRA, EULAR/ERA/EDTA and KDIGO, see Table 2) [70-72]. Recommendations on treatment dose vary (600-1500mg/m2/day up to a maximum of 3 grams/day). A lower dose of MMF can be used initially, but should be escalated to the target dose within four weeks. After 3 months of MMF treatment, both the EULAR/ERA/EDTA and KDIGO guidelines suggest that if the patient fails to show any improvement or worsens, change of therapy should be considered. Concomitant steroid treatment regimens vary between the different guidelines, and include the option of a MMF and glucocorticoid oral only induction regimen, these are shown in more detail in Table 2 .

No randomized controlled trials have been carried out in children to date, however one is currently underway assessing its use in combination with biologic therapy in LN. Evidence is limited to a non-controlled cSLE study which demonstrated MMF to be effective in improving renal function in those with membranous glomerulonephritis but not proliferative glomerulonephritis, improving disease activity and facilitating steroid tapering in both types of nephritis [73]. A retrospective case series of nine children with SLE assessing MMF as maintenance therapy for LN, has also shown it to reduce disease activity and have a glucocorticoid sparing effect [74]. Adult studies have shown MMF to be equally effective to other therapies in treating LN (III/IV) with a favourable adverse effect profile, including fertility [52].

***Cyclophosphamide***

Cyclophosphamide (CYC) is metabolized to 4-hydroxycyclophosphamide and is a potent broad-spectrum immunosuppressant with a significant adverse effect profile. It is therefore reserved only for those with severe major organ involvement where rapid disease control is required. Its beneficial effect in SLE is due to its ability to modulate 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 [52, 69, 75-77]. It’s use is recommended in cSLE LN consensus guidelines (see Table 2) [70-72] as an alternative option to MMF. Again recommendations vary, with duration of initial therapy suggested at 3-6months and dosage varying from 500-1500mg/m2 or a cumulative dose of 0.75-3g/m2 dependent on duration of therapy and the presence of prognostic factors. A European trial assessing the efficacy of a high dose (6 pulses of 500-1500mg/m2) vs. low dose (6 pulses of 500mg/m2) CYC regimen in aSLE found the low dose regimen followed by AZA to equally efficacious to a high dose regimen [78].

Table 1 highlights the adverse effects of CYC, the most concerning of which is the risk of long-term infertility. Premature gonadal failure is a concern for females commencing on CYC 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 [79]. Traditional methods to preserve fertility in adults involve the harvesting of oocytes, however ethically this is controversial in children. Gonadotropin-releasing hormone (GnRH) agonists reduce the incidence of ovarian failure in women with aSLE undergoing CYC therapy [80]. This effect is thought to arise through the 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 2 clinical trial in cSLE which has shown it to be safe and have the ability to completely suppress ovarian function [81]. Further trials to assess its efficacy are required however, if positive, may prove to be an important option. In pubertal boys sperm banking is a realistic option but must be handled in a delicate manner.

***Rituximab***

Rituximab is a chimeric anti-CD20 monoclonal antibody 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 and plasma cells, therefore its potential role for therapeutic benefit is clear. It was initially approved for treatment of Non-Hodgkin’s Lymphoma and has since been successfully tested in randomized controlled trials (RCT) in many autoimmune disorders, including rheumatoid arthritis [82-84]. B cell depletion therapy was subsequently shown to be effective in mouse models of SLE [85]. The EXPLORER trial was designed to assess the benefit of rituximab on the induction and maintenance of clinical response in adults with SLE. Disappointingly it failed to meet both its primary and secondary outcome measures [86]. The LUNAR trial investigated rituximab vs. placebo in addition to standard care (MMF and glucocorticoids) in patients with LN [87]. 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 sub-groups. There are several reasons why these trials are thought to have failed; concomitant therapy may have masked treatment effect; successful trials of rituximab used CYC which may have a synergistic effect and these trials used MMF; duration of study may not have been optimal with median time to renal response being 1-2 years and evidence has shown rituximab’s role may be as an effective alternative or adjunct in refractory disease however this was not tested [78, 88, 89].

Rituximab is the most frequently used biologic in cSLE despite robust evidence for its effectiveness being limited. It is typically reserved for either severe, intractable disease, cases that have failed other therapies or in those patients experiencing unwanted adverse effects from alternative treatments and has been recommended for this scenario by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines for LN (see Table2) [71]. A retrospective analysis of 63 patients from the UK JSLE Cohort Study over 10 years showed rituximab to reduce disease activity and steroid burden when used in those patients failing standard care, with a relatively good safety profile [90]. This has been echoed by a case series of 12 patients which showed benefit for up to 5 years [77]. Two other studies in cSLE have also demonstrated benefit in those with severe disease who have failed standard therapy [91, 92].

Addressing the previous failure of rituximab RCTs, RITUXILUP (NCT01773616) is an open labelled, multicentre RCT with the aim of demonstrating efficacy of RTX with MMF versus MMF and glucocorticoids only in LN. It will also assess this regimens 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. RING (NCT01673295) another phase III trial will also examine RTX in refractory LN and will include patients aged ≥15years.

***Belimumab***

B-cell activating factor (BAFF or B lymphocyte stimulator; BLyS) and a proliferation inducing ligand (APRIL), are members of the tumour necrosis factor ligand superfamily [93]. BAFF is present in soluble and membrane bound forms and binds to three B cell receptors; BAFF receptor, B cell maturation antigen (BCMA) and transmembrane activator and CAML interactor (TACI). It is vital for B cell survival and plays an important role in B cell maturation, immunoglobulin production and class switching [93]. APRIL is structurally similar to BAFF and is capable of binding to BCMA and TACI and has similar effects to BAFF [94]. Over expression of BAFF in mouse models leads to the development of SLE like autoimmune features, with BAFF and APRIL inhibition showing therapeutic benefit [95, 96]. BAFF levels are elevated in SLE, correlating with disease activity [97, 98]. These findings have led to the development of this class of drugs in SLE.

Belimumab is a fully humanized monoclonal antibody that binds soluble BAFF and prevents it from binding with its receptors. Two phase III clinical trials in aSLE, called the BLISS-52 and BLISS-76, assessed belimumab alongside standard SLE therapy and demonstrated a significant response with low and high dose treatment as compared to placebo together with a favourable side effect profile [99-101]. The duration of response was more sustained, steroid dose could be tapered and rates of severe flare were reduced compared to placebo at week 52 of follow up [100, 101]. Greater therapeutic benefit was found in those with auto-antibody positive disease, greater disease activity, low complement and corticosteroid use at baseline. These findings led to the US FDA and the European EMA approval of belimumab in auto-antibody positive aSLE, with NICE due to make a decision soon in the UK. However there are aspects of Belimumab treatment that require further investigation. In BLISS-76 positive effects of treatment were not sustained at 76 weeks and patients with CNS disease or severe LN were not recruited [99, 100].

Belimumab is currently undergoing a phase II randomized, double-blind trial to assess pharmacokinetics, safety and efficacy in 5-17 year old patients who have active, auto-antibody positive cSLE (The PLUTO Trial - NCT01649765). 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.

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| **Table 1 Commonly used medications with indications and side effects.** | | |
| Medication | Indications | Side effects |
| Glucocorticoids | Induction and maintenance therapy.  All moderate to severe cases; may be required for mild unremitting disease | Adrenal suppression  Striae  Obesity  Changes in mood  Growth failure  Osteoporosis |
| Cyclophosphamide | Induction therapy, usually intravenous  Moderate to severe disease with organ involvement | Infertility  Hair loss  Increased risk of infection  Nausea and vomiting  Long-term increased risk of malignancy |
| Mycophenolate mofetil | Induction and maintenance therapy  Moderate to severe disease | Abdominal discomfort  Diarrhoea  Liver inflammation  Increased risk of infection  Teratogenic in pregnancy |
| Azathioprine | Maintenance treatment  Mild, moderate or severe disease | Increased risk of infection  Bone marrow suppression |
| Methotrexate | Maintenance therapy. Musculoskeletal symptoms | Bone marrow suppression  Nausea and vomiting  Liver inflammation |
| Hydroxychloroquine | All patients | Avoid in pregnancy or G6PD deficiency |

**OTHER DISEASE CONSEQUENCES**

***Bone Health***

Children with SLE often fail to acquire peak bone mass, and more commonly have osteopenia compared to healthy children, with increased risk of developing osteoporosis as adults [102, 103]. 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 a low bone mineral density (BMD) and an increased cumulative dose demonstrates an inverse correlation with BMD [104, 105]. Therefore 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 [106].

Denosumab is a human monoclonal antibody which inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL) signalling pathway which has been shown to be a key driver of bone destruction in rheumatic disease [107]. It has been trialled across a wide range of conditions including rheumatic disorders and has a UK licence for the prevention of osteoporotic fractures in postmenopausal women and skeletal related events in adults with bone metastases from solid tumours [108]. Trials in rheumatoid arthritis have shown it to increased bone mineral density and reduce progression of bone erosions [109, 110]. A phase I/II randomized open label trial (NCT02418273) will assess its efficacy in preventing bone loss in children with rheumatic diseases, including cSLE.

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| --- | --- | --- |
| **Table 2 Summary of recommendations for treatment of Lupus Nephritis in cSLE** | | |
| **Protocol** | **Summary** | |
| **CARRA SLE Subcomittee** | **Glucocorticoids** - one of three glucocorticoid regimens (primarily oral, primarily IV, and mixed oral and IV)  AND  **Cyclophosphamide** - 6 x monthly IV CYC doses (Initial dose 500 mg/m2, subsequent doses increased not to exceed maximum monthly dose of 1,500 mg. Dose should be adjusted for renal insufficiency and a low WBC nadir  OR  **Mycophenolate –** MMF (600 mg/m2/dose twice daily with a maximum dose of 1,500 mg twice/day. A lower dose of MMF could be used at initiation of treatment, but the dose should be escalated to the target dose within four weeks of starting therapy) | |
| **KDIGO Clinical Practice Guidelines** | **Class I LN**  **Class II LN**  **Class III & IV LN**    **Class V LN**  **Class VI LN**  **Non-responders that have failed >1 recommended initial regimes** | Treat as dictated by extrarenal clinical manifestations  Proteinuria of >1 g/d , treat as dictated by the extrarenal clinical manifestations of lupus  Proteinuria >3 g/d be treated with glucocorticoids or calcineurin inhibitors  *Initial therapy*  Glucocorticoids + CYC or MMF  *Maintenance therapy*  AZA (1.5–2.5 mg/kg/d) or MMF (1–2 g/day in divided doses), and low-dose oral glucocorticoids (10 mg/day prednisone equivalent)  *Normal kidney function, and non–nephrotic-range proteinuria*  Treat as per extrarenal manifestations  *Persistent nephrotic proteinuria*  Glucocorticoids + CYC or MMF or AZA or calcineurin inhibitor  Immunosuppressants as dictated by extrarenal manifestations  Consider Rituximab, IV immunoglobulin or calcineurin inhibitor |
| **EULAR / ERA-EDTA Recommendations** | **Immunosuppressants recommended in class IIIA or IIIA/C (±V) and IVA or IVA/C (±V) nephritis, and also in pure class V nephritis if proteinuria exceeds 1 g/24hr** | |
| **Class IIIA or IIIA/C (±V) and class IVA or IVA/C (±V) LN**  **Class V LN + nephrotic range proteinuria** | *Initial Therapy*  IV methylprednisolone 3 pulses 500-750mg followed by oral prednisolone 0.5mg/kg/day for 4 weeks, reducing to <10mg /day by 4-6 months  MMF (3g/day for 6 months) or CYC (Cumulative dose 3g over 3 months or in the presence of prognostic factors 0.75-1g/m2 for 6 months or 2-2.5mg/kg/day for 3 months)  Oral prednisolone (0.5mg/kg/day) + MMF (3g/day for 6 months)  *Alternatives*  Non-responders: CYC or calcineurin inhibitor or Rituximab  Without adverse prognostic factors: AZA (2mg/kg/day)  *Subsequent Treatment - Improving*  Prednisolone (5-7.5mg/day) in combination with MMF (dose 2 g/day) or AZA (2 mg/kg/day) for at least 3 years. Gradual drug withdrawal, glucocorticoids first, can then be attempted |
| **Euro-Lupus Nephritis Trial** | **Glucocorticoids** - 3 daily pulses of 750 mg of IV 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 those with renal impairment or severe extrarenal 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 of prednisolone per day) was maintained until at least month 30.  **Cyclophosphamide High Dose -** High-dose group received 8 IV CYC pulses within a year (6 monthly pulses followed by 2 quarterly pulses). The initial CYC dose was 0.5 gm/m2; subsequent doses were increased by 250 mg according to WBC count nadir measured on day 14, with a maximum of 1,500 mg per pulse.  **Cyclophosphamide Low Dose -** Fortnightly IV CYC pulses at a fixed dose of 500 mg.  **Azathioprine -** AZA (2mg/kg/day) was started 2 weeks after the last CYC injection and continued until at least until month 30. | |

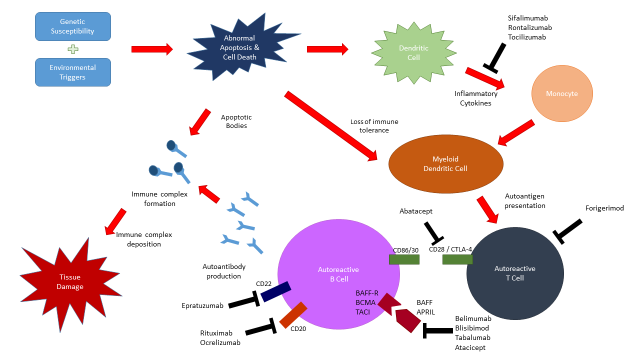
IV, Intravenous; CYC, Cyclophosphamide; MMF, Mycophenolate; LN, Lupus Nephritis; AZA, Azathioprine

**Emerging Biologic Therapies in a SLE**

Biologic agents are designed to specifically target aspects of the immune system. Figure 1 illustrates the mechanism of action of emerging biologics in relation to SLE pathogenesis. Clinical trials involving ten other biologics have been conducted in aSLE (see Table 3). At present there are no plans for these trials to be extended to cSLE. Whilst these agents show variable promise, the lack of childhood-specific studies promotes the current situation in which treatment in children is based on data from adult clinical trials. The future aim should be that medicines with potential benefit to children should be trialled in children, ideally in conjunction with adult clinical trials.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 3. Summary of Biologic Trials in aSLE** | | | | |
| Target | Drug | Molecule | RCT Phase | Summary of Evidence |
| B-Cell | Blisibimod | Anti-BAFF peptibody | III  (CHABLIS-SC1 study) | PEARL-SC (Phase IIb) study found Blisibimod to be effective vs placebo [111]. |
|  | Tabalumab | Humanized  anti-BAFF mAb | III  (NCT01205438; NCT01196091; NCT01488708) | Demonstrated efficacy in biologic naïve rheumatoid arthritis patients but failed to show benefit in patients that have previously failed anti-TNF therapy [112, 113]. |
|  | Atacicept | Anti BAFF & APRIL human fusion protein | Discontinued | Two phase II / III trials discontinued prematurely due to serious adverse events, including two fatalities [114, 115]. |
|  | Epratuzumab | Humanized anti-CD22 mAb | III  (NCT01261793; NCT01262365) | Two RCTs in patients with moderate to severe disease showed improvement vs placebo, discontinued early due to interruption of drug supply [116]. Phase IIb trial showed a non-significant benefit [117]. |
|  | Ocrelizumab | Humanized anti-CD20 mAb | Discontinued | Phase III trial discontinued early due to increased rate of serious infections [118]. |
| Interrupt B-T Cell  Co-Stimulation | Abatacept | CTLA4-Ig fusion  protein | II  (NCT02270957 ) | Phase IIb trial in non-renal lupus and lupus nephritis failed to meet primary endpoints. Post hoc analysis suggested a benefit in flare reduction, particularly in those with polyarthritis [119]. |
| T-Cell | Forigerimod | 21-mer peptide | III | Two phase II trials demonstrated safety and therapeutic efficacy [120, 121]. |
| Cytokines | Sifalimumab | Humanized anti-IFN-α mAb | II  (NCT01031836) | Reduced IFN signature but non-significant response over placebo [122]. |
|  | Rontalizumab | Humanized anti-IFN-α mAb | Discontinued | Reduced IFN signature but non-significant response over placebo [123, 124]. |
|  | Tocilizumab | Humanized IgG1  anti-IL6R mAb | No present RCT | Phase 1 trial demonstrated a significantly reduction disease activity, however there was a dose related decline in neutrophil count. Further testing required to ascertain optimal dosing [125]. |

BAFF, B-cell activating factor; mAb, monoclonal antibody; TNF, Tumour Necrosis Factor; APRIL, A Proliferation Inducing Ligand; IFN-α, Interferon-α; IgG1, Immunoglobulin-1; IL6R, Interleukin-6 Receptor



**Fig 1. Pathogenesis and Biologic Therapy in SLE.** The use of biologics in SLE employs 4 main strategies; targeting B cells; drugs interrupting B-T cell

co-stimulation; targeting T cells and anti-cytokine therapy. Although they act at different points of the immune system the common aim of therapy is to inhibit an autoimmune response.

1. **CHALLENGES FACING MANAGEMENT OF cSLE**

Despite the abundance of clinical trials being conducted with biologics in aSLE, only a minority are undertaken in cSLE. This is despite the fact that early remission can provide greater benefit in prospective years, particularly important in lifelong conditions commencing in childhood. The development of drugs for rare diseases poses logistical, economical 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 medicines for children have not been adequately studied for their purpose and therefore their use is unlicensed [126]. The United States Food and Drug Administration 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 development for children. The EU Paediatric Drug Regulation (PDR) was instituted a decade later and also provided financial incentives for paediatric research and drug development. The EU PDR has not led to a significant increase in the production of drugs for paediatric indications to date [127], however many trials are due for completion in the next few years and it will become clearer as to whether this scheme will be of patient benefit.

Clinical trials in SLE have been notoriously difficult to conduct as compared to other rheumatological conditions with several promising drugs failing either due to trial design or inability to produce the expected benefits [128, 129]. Noted issues with trial design have been identifying the correct population for the intended intervention and the importance of achieving statistical power [130]. Successful trials have employed a very large number of patients and a flexible design [130]. 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. Novel trial designs may be required to overcome this issue. The complexities of pathogenesis are vast and resources limited but it is only when this disease process is more fully understood that therapeutic advances will be made.

1. **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 immunosuppressant of varying potencies. Recent scientific advances have shed some light on the complex pathogenesis of SLE, and provided inspiration for investigation into future therapeutic targets. These have manifested in a wave of biological agents that have had much success in other autoimmune disorders but, as yet, have failed to make a significant contribution to the treatment of adult or cSLE. Information on the efficacy of biologics in cSLE is limited with just three being trialled, the results of which are not yet available. 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 trials with appropriate agents are required in children to inform and improve future management.

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