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LEADING ARTICLE

An Update on the Management of Childhood-Onset Systemic Lupus Erythematosus

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Abstract

Childhood-onset systemic lupus erythematosus (cSLE) is a prototype of a multisystemic, inflammatory, heterogeneous autoimmune condition. This disease is characterized by simultaneous or sequential organ and system involvement, with unpredictable flare and high levels of morbidity and mortality. Racial/ethnic background, socioeconomic status, cost of medications, difficulty accessing health care, and poor adherence seem to impact lupus outcomes and treatment response. In this article, the management of cSLE patients is updated. Regarding pathogenesis, a number of potential targets for drugs have been studied. However, most treatments in pediatric patients are off-label drugs with recommendations based on inadequately powered studies, therapeutic consensus guidelines, or case series. Management practices for cSLE patients include evaluations of disease activity and cumulative damage scores, routine non-live vaccinations, physical activity, and addressing mental health issues. Antimalarials and glucocorticoids are still the most common drugs used to treat cSLE, and hydroxychloroquine is recommended for nearly all cSLE patients. Disease-modifying antirheumatic drugs (DMARDs) should be standardized for each patient, based on disease flare and cSLE severity. Mycophenolate mofetil or intravenous cyclophosphamide is suggested as induction therapy for lupus nephritis classes III and IV. Calcineurin inhibitors (cyclosporine, tacrolimus, voclosporin) appear to be another good option for cSLE patients with lupus nephritis. Regarding B-cell-targeting biologic agents, rituximab may be used for refractory lupus nephritis patients in combination with another DMARD, and belimumab was recently approved by the US Food and Drug Administration for cSLE treatment in children aged > 5 years. New therapies targeting CD20, such as atacicept and telitacicept, seem to be promising drugs for SLE patients. Anti-interferon therapies (sifalimumab and anifrolumab) have shown beneficial results in phase II randomized control trials in adult SLE patients, as have some Janus kinase inhibitors, and these could be alternative treatments for pediatric patients with severe interferon-mediated inflammatory disease in the future. In addition, strict control of proteinuria and blood pressure is required in cSLE, especially with angiotensin-converting enzyme inhibitor and angiotensin receptor blocker use.

1 Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is a prototype of a multisystemic, inflammatory, heterogeneous autoimmune condition. This chronic condition is characterized by simultaneous or sequential organ and system involvement, with unpredictable flare and high morbimortality [1–24].

cSLE presentation and severity may vary according to genetic background and socioeconomic status [14]. This condition may be associated with irreversible accrual of damage, reduced health-related quality of life, and diminished life expectancy, mainly due to infections and recurrence of disease activity [18, 19].

The hallmark of cSLE is the wide spectrum of clinical and laboratory abnormalities, particularly with the production of multiple autoantibodies against histone, nonhistone, cytoplasm, and nuclear proteins, and a marked increase in proinflammatory cytokines [11, 12, 14–16]. The clinical cSLE presentation spectrum is very diverse, varying from acute, severe, life-threatening disease to chronic condition with an intermittent or continuous course, and is rarely

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Key Points

Belimumab, a monoclonal antibody that blocks the binding of soluble B lymphocyte stimulator to B cells, was recently approved by the US Food and Drug Administration for childhood-onset systemic lupus erythematosus (cSLE) treatment in children aged >5 years.

Calcineurin inhibitors (cyclosporine, tacrolimus, voclosporin) appear to be a good option for cSLE patients with lupus nephritis.

Anti-interferon therapies (sifalimumab and anifrolumab) have shown beneficial results in adult SLE patients, as have Janus kinase inhibitors, and could in the future be an alternative treatment for pediatric patients with severe interferon-mediated inflammatory disease.

New therapies targeting CD20, such as atacicept and telitacicept, seem to be other promising drugs for SLE patients.

associated with spontaneous remission without treatment [1, 2, 11].

A more aggressive course and disease flares associated with higher morbidity and mortality rates have been reported at diagnosis and follow-up in cSLE patients compared with adult-onset SLE. Indeed, cSLE patients had a higher prevalence of initial and cumulative multiorgan system involvement, such as nephritis, neuropsychiatric, hematological, and macrophage activation syndrome, than adult-onset SLE patients [13, 25–35]. In contrast, late-onset SLE (> 50 years) patients had the lowest prevalence of constitutional and mucocutaneous manifestations, serositis, and hypocomplementemia compared with cSLE and adult-onset SLE [36]. Children and adolescent patients use the same immunosuppressive agents as adult SLE patients, and generally require more aggressive treatment to achieve disease control than adult SLE populations [1, 2, 25, 28–31].

Most treatments in cSLE and adult-onset SLE are off-label drugs with recommendations based on inadequately powered studies, therapeutic consensus guidelines, or case series [1, 2, 13, 18, 19]. Racial/ethnic background, cost of medications, poor adherence, and specifically social determinants of health seem to impact lupus outcomes and treatment response [18, 19, 37].

The objective of this narrative review is to provide an update of recent new findings relevant to the management of cSLE, particularly focusing on pharmacological therapy.

2 Pathogenesis

Multiple immunologic abnormalities that occur in SLE patients are molecular targets for treatment. cSLE pathogenesis is a combination of inherited susceptibility, gestational and perinatal-related factors, hormonal changes, and environmental exposures, such as sunlight, drugs, viral infections, and air pollutants (carbon monoxide, sulfur dioxide, nitrogen dioxide, ozone, and particulate matter) [2, 38–41].

cSLE is also characterized by complex immune dysregulation, involving both innate and adaptative immunity, leading to a loss of self-tolerance followed by a sustained production of pathogenic autoantibodies targeting nuclear antigens [42, 43].

The innate immune system is responsible for a non-specific inflammatory response to pathogens. It includes a range of cells and soluble factors, such as antigen-presenting cells (APC), cytokines, and complement proteins. Dendritic cells are the main APC, and a subgroup, the plasmacytoid dendritic cells (pDC), was significantly higher in SLE patients compared with controls [44] and produce interferon (IFN) type I (IFN-1) and express toll-like receptors (TLR) 7 and 9. The endosomal TLR7 and 9 are able to detect endogenous RNA and DNA antigens [45]. Podocytes in cSLE patients with active nephritis express TLR9 and this was related to proteinuria and increased anti-dsDNA antibody [46]. Antimalarial drugs modulate the TLR7 and TLR9 signaling [47].

Importantly, the IFN-α signature is a central player in SLE pathogenesis [48–52]. IFN-α is elevated in SLE patients, particularly during disease flares, and this cytokine was increased in cSLE patients compared with their first-degree relatives and healthy controls, even in patients receiving medication [51]. IFN drives the inflammation in SLE and activates different cell types in the immune system, contributing to immunological dysregulation [53–55]. IFN-I also augments APC function and promotes apoptosis [48]. The IFN-I signature occurred in approximately 60% of cSLE patients and was associated with increased TLR7 expression of cytosolic nucleic acid binding receptors [56]. Associations were also reported between IFN-I and several markers of immune activation, such as complement, and autoantibody production, such dsDNA antibodies, which start and may also maintain SLE disease activity over time [51, 57]. Interestingly, there are now targeted therapies that can potentially modify this IFN signature (see Sect. 5).

Increased apoptosis [32, 42] and impaired clearance of apoptotic debris allow the presentation of nucleic acid self-antigens and perpetuate inflammation in cSLE [58]. The complement system is also relevant in the

degradation and removal of chromatin produced during cell death [20, 59–62]. The loss of tolerance to self-antigens in SLE can also be induced by lymphocyte abnormalities. T-cell functional and phenotypic alterations have implications in SLE pathogenesis [63]. The failure of T cells to produce IL-2 leads to a reduction in regulatory T cells and increased effector T cells, especially the T helper 17 (Th17) phenotype. This imbalance contributes to a pro-inflammatory status in adult-onset SLE and cSLE [64–66]. Additionally, changes in T-cell receptors observed in SLE result in hyperactivation of their signaling pathway [64, 67]. Azathioprine and mycophenolate mofetil are immunosuppressive agents that can interfere with T-cell function. Autoantibody production is a hallmark of lupus, and B-cell defects can account for this. B lymphocyte stimulator (BLyS) levels are elevated in cSLE [68] and contribute to a breakdown in self-tolerance. Biological agents, such as rituximab and belimumab, are B-cell pathway-targeting therapy for cSLE.

Another relevant factor in cSLE pathogenesis is genetic background, supported by 10-fold increased concordance in monozygotic compared with dizygotic twins [69]. A recent genomic DNA study including 2001 multi-ethnic SLE patients demonstrated an inverse association between age and genetic risk score involving genes outside of the HLA complex [70]. cSLE is usually a polygenic disease and more than 80 different genes in genome-wide association studies were associated with SLE [71], mainly affecting multiple pathways of the immune system [42, 64, 72].

Furthermore, single gene defects associated with cSLE are very rare [73], involving different immune pathogenetic pathways, such as the complement system, phagocyte oxidase system, apoptosis, nucleic acid repair, DNA degradation, DNA sensing, type I IFN, and B-cell development [74, 75]. Inborn errors of immunity are caused by monogenic mutations, resulting in loss or gain of function of the encoded protein, and may present as increased susceptibility to infectious diseases, allergic, malignant, autoinflammatory and autoimmune conditions [76].

Genetic analysis to assess monogenic lupus (whole exome or whole genome sequencing) is very important to improve the knowledge of the genetic basis and increase options for new drug targets and biomarker development [77], and therefore should be considered for cSLE patients with early onset of lupus manifestations (mainly in infants and toddlers with cSLE) [78]. Patients with the gene defect have a specific disease presentation and progression [79], such as recurrent infection and prominent cutaneous manifestation, requiring personalized management.

3 Childhood-Onset Systemic Lupus Erythematosus (cSLE) Stratification and New Validated Classification Criteria

Lupus is a very heterogeneous disease and the response to treatment is very difficult to predict. This heterogeneity is one of the reasons for the high failure rate of target therapy trials. Stratification schemes and accurate classification criteria of cSLE patients represent potential ways of refining cSLE clinical trials [80].

Studies evaluating cSLE stratification at disease onset and during the disease course have been reported to differentiate clinical and laboratory abnormalities according to age and diagnostic delay [20–22, 81, 82].

A large, retrospective, multicenter cohort study in Brazil assessed demographic data, clinical manifestations, and laboratory exams at disease diagnosis in three age groups of cSLE: early-onset (< 6 years), school-age (≥ 6 and < 12 years), and adolescent (≥ 12 and < 18 years). Fever, hepatomegaly, and splenomegaly occurred more often in the early-onset group, and weight loss, photosensitivity, and leukopenia/lymphopenia in the adolescent group [20]. Similarly, a British cohort assessed cSLE patients based on age at disease presentation: pre-pubertal (< 7 years), peripubertal (8–13 years), and adolescent groups (14–18 years). The adolescents had lower levels of white cell count, and higher frequencies of disease activity, low complement levels, antinuclear antibodies (ANA) positive, and anti-dsDNA titers compared with the other groups [81]. Regarding the accrual damage at the last follow-up, both the Brazilian and British cSLE groups demonstrated that disease damage scores were comparable between the age groups [22, 81].

The Brazilian registry assessed 1533 cSLE patients based on three groups with different periods between the onset of signs/symptoms and the diagnosis. This study revealed cSLE patients infrequently had a shorter time interval to diagnosis (< 1 month) characterized by multisystemic, severe, and active conditions, whereas the majority of cSLE patients had a long-time interval (≥ 3 months) to diagnosis, with mild disease onset [21].

Three classification criteria have been proposed for SLE patients to use in daily clinical practice, research, and clinical trials [83, 84]. The American College of Rheumatology classification criteria modified in 1997 (1997-ACR) are the most universally used for cSLE patients [19, 83]. In 2012, the Systemic Lupus International Collaborating Clinics (2012-SLICC) group published a new set of classification diagnostic criteria, including a stand-alone renal criterion for cSLE patients with biopsy compatible with lupus nephritis and positive ANA or anti-dsDNA antibodies [84].

Studies compared the performance of these two sets of criteria in pediatric lupus populations [85–88] and reported a higher sensitivity for the 2012-SLICC criteria [85–88] and higher specificity for the 1997-ACR criteria. A recent meta-analysis established that the 1997-ACR criteria had the best overall performances for cSLE, even if associated with lower sensitivity [89]. In 2019, the European League Against Rheumatism (EULAR) and the ACR developed new classification criteria for systemic lupus preserving the specificity of the 1997-ACR and the sensitivity of the SLICC criteria in adult SLE [90]. The 2019 EULAR/ACR classification criteria proposed weighted criteria grouped in seven clinical and three immunological domains, using ANA positive as a mandatory entry criterion. A score of ≥ 10 classifies a patient as SLE [90].

Three recent reports evaluated 2019-EULAR/ACR classification criteria in cSLE patients. The 2019-EULAR/ACR criteria effectively classify cSLE, irrespective of age, sex, and race, and these new criteria were more sensitive (85% vs 72%) with comparable specificity in youths with SLE compared with the 1997-ACR criteria (83% vs 87%) [91]. Another study showed the same sensitivity for 2019-EULAR/ACR and 2012-SLICC criteria (97.4%) and it was higher compared with the 1997-ACR criteria in cSLE patients (87.2%), with similar specificity between 2012-SLICC and 2019-EULAR/ACR criteria (98.4% and 99.7%, respectively) [92]. Fonseca et al. showed that a 2019-EULAR/ACR total score ≥ 13 was more appropriate to classify Brazilian cSLE patients than the proposed score of ≥ 10 and that 2012-SLICC criteria better scored for cSLE at the first visit and 1-year-follow-up [93].

4 Monitoring Disease Activity and Damage

Disease activity evaluation includes different reliable and valid instruments for use in academic and clinical practice for cSLE [2, 94, 95]. The most important validated overall disease activity scores are Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), British Isles Lupus Assessment Group (BILAG), and Medical Global Assessment of Disease Activity (MD Global) [94].

Recently, European evidence-based recommendations for diagnosis and treatment of cSLE and childhood-onset lupus nephritis were established by consensus meetings [96, 97]. One of these recommendations was that all cSLE patients should have disease activity parameters evaluated regularly in clinical practice, using one of the two standardized validated disease activity instruments: SLEDAI 2000 (SLEDAI-2K) or pediatric BILAG index 2004 (pBILAG-2004) [96]. Therefore, disease activity tools should be used at cSLE diagnosis and during the disease course.

There is a new description of low disease activity in SLE patients. The definition of lupus low disease activity state (LLDAS) includes SLEDAI-2K ≤ 4, without any activity in major organ systems and no new features of activity compared with the previous evaluation, Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI physician global assessment ≤ 1; current prednisolone dose ≤ 7.5 mg/day and standard maintenance doses of immunosuppressants and approved biological drugs [98]. Importantly, this parameter has proven to be associated with a decrease in SLE flares, reduced risk of disease damage, and may be used as a treat-to-target approach in daily clinical practice and for future SLE clinical trials [99]. A prospective validation study with 1707 adult SLE patients showed that the percentage of subjects with accrual damage was significantly lower in patients who achieved sustained LLDAS compared with those that never experienced sustained LLDAS (2.9% vs 17.8%) [100]. Further prospective multicenter studies will be necessary to assess LLDAS in cSLE populations.

Recent provisional criteria for global flares in cSLE patients were also established after consensus formation methodology with pediatric rheumatologists and pediatric nephrologists, and defined threshold levels for minor, moderate, and major flares. These criteria included the most important disease activity scores and inflammatory markers, and they are therefore relevant for measuring systemic responses to interventions intended to treat systemic or organ-specific involvements of cSLE patients. One of these criteria was the SLEDAI-based algorithm ($0.5 \times \Delta$SLEDAI $+ 0.45 \times \Delta$protein/creatinine ratio $+ 0.5 \times \Delta$MD-global $+ 0.02 \times \Delta$erythrocyte sedimentation rate), and flare scores of ≥ 6.4/3.0/0.6 comprised major/moderate/minor flares, respectively. The other criterion was based on BILAG algorithm ($0.4 \times \Delta$BILAG $+ 0.65 \times \Delta$protein/creatinine ratio $+ 0.5 \times \Delta$MD-global $+ 0.02 \times \Delta$erythrocyte sedimentation rate), and flare scores of ≥ 7.4/3.7/2.2 constituted major/moderate/minor flares, respectively [101]. These criteria are relevant instruments for future use in clinical trials, allowing longitudinal assessment of cSLE patients and measurement of overall disease course since existing treatments used in cSLE are not uniformly effective in reducing disease activity [101].

In addition, the same international consensus with pediatric rheumatologists and nephrologists also established a provisional index of clinically relevant improvement in cSLE. This is an important instrument to assess response to treatment and to classify the degree of improvement as minor, moderate, or major [102].

Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score evaluates cumulative damage, indicating an

overall measurement of disease activity and severity in SLE patients. This score is validated for pediatric lupus patients and has been demonstrated to be a valid and reliable instrument for cSLE [2]. It is a mainly disease-related outcome, while treatment with glucocorticoids, immunosuppressive and biological agents are also risk factors for increased damage score [2, 22].

A pediatric version of SDI is also available for clinical practice in cSLE, including two additional domains: growth failure and delay in secondary sexual characteristics [103]. European evidence-based recommendations for diagnosis and treatment of cSLE also suggested that patients with cSLE should have cumulative damage assessed yearly using a standardized damage parameter, primarily using pediatric SDI [96].

The SDI instrument is the sum of SDI item scores. The frequency of SDI score ≥ 1 ranged from 28% to 52% of cSLE populations, generally evidenced after 2–4 years of diagnosis [104, 105]. A recent, international multicenter study including 1048 cSLE patients with a mean disease duration of 3.8 years evidenced that almost half the patients had disease-related damage measured by SDI score. The most frequently scored items were proteinuria, scarring alopecia, and cognitive impairment [106]. Neuropsychiatric and renal involvements were the main predictors of higher damage accrual over time in another report [107].

Two other prospective studies from Canada and the Netherland assessed the long-term outcomes of adult SLE patients with pediatric onset. A longitudinal damage study with 473 SLE patients showed that baseline features, Afro-Caribbean ethnicity, short diagnosis lag time, and the presence of major organ and system involvements (lupus nephritis class III/V, cerebrovascular accidents, vasculitis, alveolar hemorrhage, and/or myocarditis) were significantly associated with more damage [108]. Another study of 111 cSLE patients with median disease duration of 20 years demonstrated that acute cerebrovascular accident, renal transplantation, replacement arthroplasties, and acute myocardial infarction were evidenced in the ages of 20 years, 24 years, 34 years, and 39 years, respectively [109]. Since the mortality rate of SLE has progressively decreased in the last decades [110], the prevention of organ damage is one of the main goals in the management of cSLE patients, including early diagnosis, multidisciplinary approach, and aggressive treatment.

5 Management Data and Drugs for cSLE

The goals of cSLE treatment are to alleviate signs and symptoms, control disease activity, minimize drug-induced adverse events, prevent long-lasting damage, and improve health-related quality of life. Immunomodulation and immunosuppression are the main focus of pharmacological management, and specific therapy should be individualized according to the manifestations and severity of the disease. cSLE management requires a multidisciplinary and multiprofessional team, led by a qualified pediatric rheumatologist who can co-ordinate the patient's support with all pediatric subspecialties [1, 2, 13]. Presently, there is a lack of high-quality evidence of multinational clinical trials, and therefore the majority of treatments have been adapted from adult protocols and are mainly established by clinical experience, clinical practice guidelines, and retrospective case series [2, 13, 66, 111].

Health quality measures are tools used by care management organizations to provide high-quality health care for patients [112]. International consensus recommendations for care of cSLE patients included nine quality indicators: diagnostic testing, education of cardiovascular risk and lifestyles, lupus nephritis, bone health, ophthalmologic examination, medical transition to adult clinic care, pregnancy, medication management, and immunization [113]. A further multicenter and multinational study including 483 cSLE showed that larger tertiary pediatric rheumatology centers tended to meet these cSLE quality indicators and offer standards of medical care more often than smaller centers. Notably, assessment of bone mineral density in patients exposed to glucocorticoids ranged widely among the centers involved (7–90%), and some centers reported low accessibility to kidney biopsies [114].

5.1 General Treatment

General management practices for cSLE patients include sunscreen protection, a well-balanced diet with low salt and adequate calcium consumption, and immunization against common pathogens [2]. Due to immune dysregulation and immunosuppressive treatment, cSLE patients have a marked increased risk of infections. Indeed, infections are one of the most common causes of mortality and can induce a disease flare in these patients [22]. Therefore, immunization is a powerful tool to reduce the burden of infectious diseases in the clinical management of cSLE and is recommended to be undertaken prior to the initiation of immunosuppressive treatment for all patients. Routine non-live vaccinations are strongly suggested for all children and adolescents with cSLE, such as influenza, tetanus, hepatitis A and B, meningococcal, pneumococcal, quadrivalent human papillomavirus vaccinations, and COVID-19 [115, 116]. Live attenuated immunizations (such as varicella-zoster; measles, mumps and rubella; and yellow fever vaccines) are generally not indicated for immunosuppressed cSLE patients [2]; however, no severe events with live-attenuated viruses were reported in a case series of vaccinated cSLE patients under immunosuppressive agents, after the measles, mumps and

rubella and varicella-zoster booster vaccinations [117]. Non-live vaccines against COVID-19 may be used in young and adult patients with rheumatic diseases under immunosuppressive/immunomodulating therapy [118]. The potential risks of vaccines against COVID-19 remain unknown for adult-onset SLE patients and the optimal dose for efficacy may be different from that in healthy subjects, however, the risks of not receiving the immunization are far greater currently [119]. Preliminary data for one COVID-19 immunization (messenger RNA vaccine) in a placebo-controlled trial of 2200 adolescents aged 12–15 years showed 100% efficacy and a strong immune response [120]. This may be relevant to efforts to control the pandemic, since this group of patients may have a role in viral transmission [121] and a distinct phenotype from adults with less symptomatic disease [122]. Further studies to confirm these data and to assess the medium and long-term effectiveness and safety of the COVID-19 vaccine in pediatric rheumatic diseases are eagerly awaited since widespread vaccination is the most efficacious tool to fight against this global pandemic. Table 1 illustrates vaccines that are indicated and contraindicated in the clinical practice of immunosuppressed cSLE patients.

Strict control of blood pressure is periodically required. A recent study reported arterial hypertension in approximately one-third of cSLE patients, almost 3 years after the disease onset. In multivariate analysis, lupus nephritis, obesity, and high frequency of extra-renal disease activity were independent predictors of arterial hypertension at baseline [123]. Prompt adjuvant treatment of arterial hypertension and proteinuria should be recommended for all cSLE patients [96]. Renin–angiotensin–aldosterone system blockade antihypertensive and antiproteinuric effects are particularly important in SLE management [124]. Proteinuria is a strong predictor of long-term renal outcomes [125]; consequently, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) use is considered a renoprotective strategy [126] and recommended for all SLE patients with arterial hypertension or with proteinuria (urine protein:creatinine ratio > 50 mg/mmol) [124, 127, 128]. A recent study demonstrated that the combination of ACE-I and ARB had good tolerability and was without significant adverse events in adult SLE, such as worsening of renal function and hyperkalemia [126].

Physical activity should be recommended for cSLE treatment on a routine basis [129]. Pinto et al. showed that cSLE patients, including those with mild and inactive disease, had impaired aerobic capacity and reduced health-related quality of life parameters compared with healthy controls matched by physical inactivity, age, sex, and body mass index [130].

Management issues related to mental health, particularly anxiety, depression, and ineffective family coping, are frequent in children and adolescents with cSLE or lupus nephritis patients and may impact their health-related quality of life [131, 132]. Although there is a lack of controlled studies assessing mental issues in cSLE, studies report depression and anxiety symptoms to be present in 37% and 30% of patients, respectively [133], and to be more frequent during the induction phase of the treatment [131]. Identifying targets for improving mental health care, such as developed mental health training for pediatric rheumatologists and integration of medical and mental health services, was proposed by CARRA (Childhood Arthritis and Rheumatology Research Alliance) [132]. Therefore, monitoring and referrals for mental health staff in cSLE patients are warranted.

5.2 Immunomodulation and Immunosuppression

Antimalarial drugs are the backbone of the immunomodulatory regimen used to treat cSLE patients and are an effective steroid-sparing treatment [134]. The benefits of hydroxychloroquine (HCQ) on autoimmune disorders have been known for many decades [47], and this drug may interfere in the inhibition of TLR7 and TLR9 signaling, dendritic cell function, and binding of antiphospholipid

Table 1 Indications and contraindications of vaccine use for cSLE clinical practice

Immunizations	Type of vaccine
Non-live vaccines are strongly indicated for immunosuppressed cSLE patients	Influenza vaccine
	Tetanus vaccine
	Hepatitis A and B vaccines
	Meningococcal vaccine
	Pneumococcal vaccine
	Quadrivalent human papillomavirus vaccine
	COVID-19 vaccine
Live-attenuated vaccines are generally contraindicated for immunosuppressed cSLE patients	Varicella-zoster vaccine
	Measles, mumps and rubella (MMR) vaccine
	Yellow fever vaccine

COVID-19 2019 coronavirus disease, *cSLE* childhood-onset systemic lupus erythematosus

antibody-β2-glycoprotein I complexes [135]. The Single Hub and Access point for pediatric Rheumatology in Europe (SHARE) recommendations for diagnosis and treatment of cSLE suggest that all cSLE patients should be on HCQ regularly [96], and the HCQ prescription is considered a quality measure indicator for cSLE treatment [136]. In line with these recommendations, a recent retrospective inception cohort with 473 cSLE patients showed that antimalarial exposure 6 months before each visit protected against an increase in SDI damage score [108]. Another study observed that current HCQ monotherapy was associated with the absence of damage (SDI score of 0) in a cohort of adults with cSLE that assessed long-term clinical outcomes [109].

Retinopathy is the most important adverse event of HCQ. The 2016 revision recommendations on screening for HCQ retinopathy from the American Academy of Ophthalmology proposed a baseline ophthalmologic examination (automated visual fields and spectral-domain optical coherence tomography) for all lupus patients during the first year of starting HCQ and annual screening after 5 years. The main risk factors for retinopathy are daily dosage > 5 mg/kg (with an additional risk annually), renal disease and underlying retinal disease [137]. In contrast, many pediatric practitioners recommend annual eye screening for cSLE patients, reinforced by the SHARE guidelines, especially for those under HCQ treatment [96].

Glucocorticoids (GC) are an effective anti-inflammatory and immunosuppressive drug for cSLE therapy, often necessary for rapid disease control, and should be limited in dose and duration to what is clinically necessary. The most important GC mechanism of action is the activation of cytosolic glucocorticoid receptors, interfering in the transcription of nuclear factor-kB and decreasing the synthesis of pro-inflammatory proteins. Non-genomic pathways of GC also play an important role in the anti-inflammatory effects, especially with high-dose pulse glucocorticoid therapy [138]. In addition, glucocorticoids stimulate apoptosis in many cell types, including pDC. However, chronically stimulated pDC through TLR7 and 9 are more resistant to glucocorticoid-induced apoptosis and this contributes to the reduced therapeutic activity of oral glucocorticoids. In contrast, intravenous methylprednisolone pulse therapy may normalize the IFN signature and is associated with a reduction in the number of circulating pDC [139]. Prolonged and high-dose use of GC should be strictly avoided due to the significant adverse events, particularly in children and adolescents [2]. Indeed, a recent longitudinal study demonstrated that adults with childhood-onset disease had significantly higher steroid-related damage compared with those who had disease onset after 18 years old (OR 1.7, 95% CI 1.1–2.8) [140]. Dosages of GC ≥ 7.5 mg/day were associated with cataract, osteoporotic fractures, and cardiovascular damage in SLE patients [141]. Furthermore, the glucocorticoid effect on chondrocytes and the hypothalamic-pituitary-gonadal axis interferes in the developmental stage of adolescence and impacts final height and puberty [142–144]. In a retrospective cohort of 97 cSLE patients, 23% of the participants were classified as having short final height and they had a higher cumulative corticosteroid dose compared with those with normal final height [143]. Rygg et al. showed that delayed pubertal onset was observed in 15.3% of females with cSLE and 24% of males [144].

Specific immunosuppressives should be customized for each patient based on disease flare and cSLE severity [2]. Lupus nephritis is the leading cause of morbidity in cSLE patients [22, 109] and immunosuppressive therapy includes induction and maintenance. Recently, the SHARE initiative [97] and Latin American Group for the Study of Lupus (GLADEL) and Pan-American League of Associations of Rheumatology (PANLAR) published recommendations for childhood-onset lupus nephritis treatment [18]. For lupus nephritis classes I and II, low-dose prednisone and antimalarials are first-line therapy [2], and disease-modifying antirheumatic drugs (DMARDs) should be used in the event of persistent proteinuria or failure to taper GC after 3 months [97]. For lupus nephritis classes III and IV, mycophenolate mofetil or intravenous cyclophosphamide (IVCYC) in combination with corticosteroids are recommended as induction therapy, while mycophenolate mofetil or azathioprine are suggested as maintenance therapy for 3 years [18, 97]. For pure membranous lupus nephritis (class V), the SHARE expert group suggests induction treatment with mycophenolate mofetil in combination with low-dose oral prednisone, and mycophenolate mofetil or azathioprine as maintenance therapy [97].

Nevertheless, cSLE patients with refractory disease or with a severe adverse event to standard therapies require additional treatment [2, 66, 97, 134]. Although there is limited evidence for rituximab use in children and adolescents with cSLE, a recent systematic review suggested that this B-cell-targeting biologic agent was safe and improved disease activity, serum and urine disease activity markers, and reduced GC dose in cSLE patients [145]. The SHARE group also recommended rituximab for refractory lupus nephritis patients in combination with another DMARD [97]. Recently, rituximab was also effective as second-line therapy for refractory autoimmune hematological disease in cSLE patients [146], and in a small case series of childhood-onset lupus erythematosus panniculitis [147].

Specific immunosuppression should also be matched to disease manifestations, not just flare, and overall severity. The combination of cyclophosphamide and rituximab has been reported more widely in cSLE [148]. Another case report involving three cases demonstrated that a combination of rituximab and abatacept was a strategy for repetitive

B-cell depletion in children and adolescents with severe autoimmune diseases, including two cSLE patients [149].

Belimumab is a monoclonal antibody that blocks the binding of soluble BLyS to B cells. This B-cell pathway-targeting agent was recently approved by the US Food and Drug Administration (FDA) for cSLE treatment in children > 5 years of age [134, 150]. Importantly, a randomized, double-blind, placebo trial evaluated the efficacy and safety of intravenous belimumab (10 mg/kg) plus standard therapy versus placebo in cSLE patients. The main exclusion criteria were active neuropsychiatric lupus, acute severe lupus renal involvement, and prednisone > 1.5 mg/kg/day. A greater proportion of patients receiving this biologic therapy met the primary efficacy endpoint of SLE responder index (SRI4) response rate (52.8% vs 43.6%; OR 1.49 [95% CI 0.64–3.46]). The improvement in Pediatric Rheumatology International Trials Organization/American College of Rheumatology (PRINTO/ACR) response using 50 definitions was also significantly higher in the belimumab group (60.4% vs 35.0%; OR 2.74 [95% CI 1.15–6.54]). Serious adverse effects were observed in 17% of the belimumab group and 35% of the placebo group, and none of them developed anti-belimumab antibodies. However, a limitation of this study was the small sample size to identify a statistically significant difference in the primary outcome [151]. The use of belimumab for cSLE patients was reported by 11% (18/161) of surveyed Latin America Pediatric Rheumatologists [19]. Further multicenter and multinational studies with this biologic drug in a large cSLE population will be required.

There are new therapies targeting CD20 in SLE patients. Atacicept and telitacicept are anti-CD20 monoclonal antibody agents that inhibit both BAFF (B-lymphocyte Activating Factor of the tumor necrosis factor Family) and APRIL (A PRoliferation-Inducing Ligand), both are relevant B-cell regulator cytokines, and anti-BAFF and APRIL therapies seem to be promising drugs for SLE patients [152].

Anti-IFN therapies, such as sifalimumab (anti-IFN-α monoclonal antibody) and anifrolumab (a monoclonal antibody that binds to a type I IFN receptor) have shown beneficial results in phase II randomized control trials in adult SLE patients with moderate-severe disease versus placebo in addition to standard-of-care medications, without severe nephritis and neuropsychiatric involvement [153–155]. A recent case report of three cSLE patients allergic to rituximab demonstrated that ofatumumab, a fully humanized anti-CD20 monoclonal antibody, was a safe, well tolerated, and effective alternative for B-cell depletion [156]. Another report suggested Janus kinase (JAK) inhibitors as an alternative treatment for pediatric patients with severe IFN-mediated inflammatory disorders, including cSLE patients, reducing progressively inflammatory markers, IFN score, and inducing upregulation of the DNA repair pathway [157].

Calcineurin inhibitors (cyclosporine, tacrolimus, voclosporin) have both immunomodulatory and non-immune-mediated roles in treating SLE. They inhibit T-cell proliferation in addition to non-immunological effects that reduce proteinuria, including podocyte cytoskeleton stabilization and afferent arteriole vasoconstriction [158]. According to the SHARE recommendation, tacrolimus and ciclosporin can be an option for selected lupus nephritis patients [97].

Calcineurin inhibitors have been studied within a multi-target treatment in proliferative lupus nephritis, particularly in the Asian population. In a randomized controlled trial including 368 SLE patients also treated with intravenous methylprednisolone pulse therapy and oral prednisone, the overall response was higher in SLE patients receiving 24 weeks of mycophenolate mofetil (1 g/day) plus tacrolimus (4 mg/day) versus those receiving intravenous cyclophosphamide (84% vs 63%). The incidence of adverse events was similar in both groups [159]. Voclosporin has been studied in a phase II, multicenter, randomized, double-blind, placebo-controlled trial of induction therapy for lupus nephritis, in combination with mycophenolate mofetil and rapid corticosteroid tapering. Among 265 geographically diverse lupus nephritis patients at 6 months, the multi-target therapy achieved superior remission rates (27–33%) compared with placebo (19%); however, higher rates of adverse events including death were reported [160]. A meta-analysis of 45 randomized trials involving 4222 SLE patients with proliferative lupus nephritis, including children and adolescents with cSLE, also showed higher remission rates with mycophenolate mofetil, calcineurin inhibitors, and their combination than with intravenous cyclophosphamide. Mycophenolate mofetil was the most effective maintenance treatment [161]. Furthermore, in a randomized trial of 28 SLE patients with pure membranous lupus nephritis, greater response rates at 6 months were reported with glucocorticoid and tacrolimus compared with SLE patients with glucocorticoid and mycophenolate mofetil (100% vs 75%) [162]. Therefore, although longer-term outcomes are required, calcineurin inhibitors seem to be a good option for cSLE patients with lupus nephritis.

Table 2 includes the main steroid-sparing immunomodulatory and immunosuppressive agents used in clinical practice for the management of cSLE patients. Serious adverse events are an important aspect of clinical care, counseling, and monitoring for cSLE patients. The most relevant major serious adverse events of immunosuppressive agents are found with azathioprine (infection and bone marrow suppression), methotrexate (hepatotoxicity, gastrointestinal intolerance, and bone marrow suppression), mycophenolate mofetil (infection, bone marrow suppression), cyclophosphamide (infection, decreased ovarian reserve, sperm abnormalities, bone marrow suppression, malignancy), rituximab (infection, infusion reaction, persistent

Table 2 The main steroid-sparing immunomodulatory and immunosuppressive agents used in the clinical practice of cSLE patients

Medications	Usual dose	Major indications	Major serious adverse events
Hydroxychloroquine[a]	5 mg/kg/day (maximum 400 mg/day), orally	All patients without contraindication [126]	Retinopathy
Azathioprine	2–3 mg/kg/day (maximum 150 mg/day), orally	Steroid-sparing for mild/moderate disease	Infection
		Maintenance therapy in LN [18, 96]	Bone marrow suppression
Methotrexate	15–20 mg/m^2/week orally or subcutaneously	Steroid-sparing in mild/moderate disease, especially with musculoskeletal involvement [67, 95]	Hepatotoxicity GI intolerance Bone marrow suppression
Mycophenolate mofetil	1200–1800 mg/m^2/day (maximum 3000 mg/day), orally	Induction and maintenance therapy in proliferative and membranous LN	Infection
		Neuropsychiatric disease	Bone marrow suppression
		Steroid-sparing in moderate/severe disease [18, 95, 96]	
Cyclophosphamide	500 mg/dose (six doses, every 2 weeks, therapy duration of 3 months) OR 500–750 mg/m^2/dose (6 monthly doses), intravenous, therapy duration of 3 years	Severe disease	Infection
		Induction therapy in proliferative LN [18, 95, 96]	Decreased ovarian reserve Sperm abnormalities Bone marrow suppression Malignancy
Rituximab	750 mg/m^2 (2 doses, with interval of 14 days) OR 375 mg/m^2/week (4 doses with interval of 7 days), intravenous, therapy duration of 1 month	Severe and refractory disease [95, 96, 129, 132]	Infection Infusion reaction Persistent hypogammaglobulinemia
Belimumab[a,b]	10 mg/kg every 4 weeks, intravenous	Clinically active disease, without active neuropsychiatric cSLE or acute severe lupus renal involvement [134, 135]	Infection

cSLE childhood-onset SLE, *GI* gastrointestinal, *LN* lupus nephritis, SLE systemic lupus erythematosus

[a]Treatment formally approved for adults with SLE

[b]Treatment formally approved for cSLE

hypogammaglobulinemia), and belimumab (infection) [1, 2, 13, 151, 163] (Table 2).

6 cSLE Prognosis Factors

Knowledge of cSLE prognosis factors is relevant to disease management since predictive factors of the long-term renal outcome at early stages of SLE are important to define clinically relevant targets of drug intervention [164]. Three laboratory or urinalysis tests have been used regularly in clinical practice as noninvasive predictors for cSLE renal involvement: kidney function (serum creatinine levels and measurement of glomerular filtration rate), urinary protein excretion, and glomerular hematuria [15, 165].

Early decrease of 24-hour proteinuria (< 0.8 g/day) is the best predictor of long-term nephritis outcome in SLE patients, based on two previous trials in adult lupus nephritis [166, 167]. Decreased proteinuria at 1 year of follow-up was also the only predictor of renal outcome at 7 years observed in a Latin American SLE group with severe biopsy-proven lupus nephritis [125]. Another study demonstrated that both proteinuria and serum creatinine levels at 1 year were important to predict relevant long-term outcomes in lupus nephritis, while urinalysis did not add value [168].

In cSLE populations, decreased creatinine clearance rate and low C3 complement levels with high serum creatinine levels were associated with end-stage renal disease [169]. A recent study, including 26 previous reports, showed that high serum creatinine (> 1.5 mg/dL) at disease presentation was the major prediction factor for progression to end-stage renal disease [170]. Furthermore, high titers of anti-dsDNA antibodies have modest accuracy to predict lupus nephritis [171].

Novel urinary and serum non-invasive biomarkers were reported to be promising parameters to predict disease outcome, disease activity, and to estimate chronic kidney damage in adult and cSLE patients [165]. A prospective study in cSLE patients with nephritis showed that urinary NGAL (neutrophil gelatinase-associated lipocalin) was a predictor of impaired renal disease activity, contrasting with urinary monocyte chemo-attractant protein 1 (uMCP1) that was a

predictor of improved lupus nephritis [172]. Another longitudinal report assessed whether urinary levels of ten biomarkers were related to chronic kidney damage in pediatric lupus nephritis. Renal functional impairment was more evidenced in cSLE patients with persistent high levels of transforming growth factor-β (TGFβ), transferrin, and liver fatty acid-binding protein (LFABP), indicating persistent renal inflammation. Levels of osteopontin and adiponectin measured at the time of kidney biopsy in cSLE patients are good predictors of histological damage with lupus nephritis [173]. Comorbidities in cSLE patients, such as arterial hypertension or diabetes mellitus, may also alter the excretion of urinary and serum non-invasive biomarkers, even in the absence of histologic changes [165]. Further longitudinal and multicenter studies will be necessary to identify and validate these biomarkers for disease activity monitoring and to predict disease severity in different renal histology patterns.

7 Drug Adherence for Adolescents

cSLE patients are mainly in the adolescence period [20]. This transitional phase to adulthood involves several physical and emotional changes [37], and the impact of this complex disease may affect their self-management and self-esteem [174, 175]. In fact, a cSLE study in adolescents and young adults with a semi-structured interview showed that the use of medication served as reminders of their illness and made them feel abnormal [176]. Nonadherence to medication in cSLE adolescents was a relevant issue in clinical practice, reported by 97% of Latin American pediatric rheumatologists [19].

There are factors associated with nonadherence to drug therapy in cSLE and other chronic rheumatic conditions, including forgetfulness, low socioeconomic status, family disruption, polypharmacy, and psychiatric comorbidities [37, 177, 178]. Poor compliance contributes to negatives outcomes and decreases the health-related quality of life [179–181]. Scalzi et al. created an online educational program for a cohort of SLE adolescents and young adults. The percentage of drug adherence using web-based education with social media intervention improved significantly from 50 to 92% [182]. A recent systematic review study assessed mobile health technologies to support the management of cSLE and adult SLE, and it demonstrated that currently available instruments were of poor quality and limited functionality [183].

Thus, it is recommended that medication adherence should be checked during the pediatric rheumatologist appointments, especially before any decisions around treatment modifications [2, 96]. Understanding and responding to adolescent demands with a personalized treatment plan and multidisciplinary teams, including psychological/psychiatric support, health education strategies, and adherence interventions may help cSLE teens to increase compliance with treatment [37, 174, 176, 181, 182].

8 Conclusions

cSLE is the prototype of a multisystemic, chronic, inflammatory, and heterogeneous autoimmune condition. This disease is characterized by concomitant or further organ and system involvement, with unpredictable flare and high morbimortality. Whole exome or whole genome sequencing should be considered for cSLE patients to exclude monogenic lupus, particularly in those with early onset of manifestations. Consultation with a geneticist or genetic counselor for such testing should be recommended. Age subgroups may help cSLE stratification at disease onset and during the disease course. The new 2019-EULAR/ACR classification criteria have high sensitivity and high specificity for cSLE, and recent provisional criteria for global flares and a provisional index of clinically relevant improvement have been developed for cSLE patients. Nonadherence to medication in cSLE adolescents was identified as one of the most relevant issues in clinical practice. Belimumab was recently approved by the FDA for cSLE treatment in children aged > 5 years. Recognition that cSLE is a potentially aggressive disease with high morbidity and mortality rates is an essential step towards the development of safer and more efficacious treatments. The treat-to-target principle and tailored medicine approaches are novel paradigms for treatment and should also be standardized for pediatric lupus patients.

Declarations

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