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Systemic Lupus Erythematosus: Diagnosis and Clinical Management

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Abstract

Systemic lupus erythematosus (SLE) is a worldwide chronic autoimmune disease which may affect every organ and tissue. Genetic predisposition, environmental triggers, and the hormonal milieu, interplay in disease development and activity. Clinical manifestations and the pattern of organ involvement are widely heterogenous, reflecting the complex mosaic of disrupted molecular pathways converging into the SLE clinical phenotype. The SLE complex pathogenesis involves multiple cellular components of the innate and immune systems, presence of autoantibodies and immunocomplexes, engagement of the complement system, dysregulation of several cytokines including type I interferons, and disruption of the clearance of nucleic acids after cell death. Use of immunomodulators and immunosuppression has altered the natural course of SLE. In addition, morbidity and mortality in SLE not only derive from direct immune mediated tissue damage but also from SLE and treatment associated complications such as accelerated coronary artery disease and increased infection risk.

Here, we review the diagnostic approach as well as the etiopathogenetic rationale and clinical evidence for the management of SLE. This includes 1) lifestyle changes such as avoidance of ultraviolet light; 2) prevention of comorbidities including coronary artery disease, osteoporosis, infections, and drug toxicities; 3) use of immunomodulators (i.e. hydroxychloroquine and vitamin D); and 4) immunosuppressants and targeted therapy. We also review new upcoming agents and regimens currently under study.

Keywords

systemic lupus erythematosus; diagnosis; management

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1 Introduction

Systemic lupus erythematosus (SLE) is the quintessential autoimmune disease. A complex interaction of impaired apoptotic clearance, upregulation of innate and adaptive immune system, complement activation, immune complexes, and tissue inflammation culminates in a self-sustained autoimmune process. Multiple pathogenic mechanisms likely can converge toward the clinical phenotypes that we call SLE. In fact, while many organs and tissues may be affected by SLE, the pattern of clinical manifestations and autoimmune phenomena is heterogenous among patients and even changes over time in individual patients. For this reason, diagnosis is often difficult or delayed and relies on keen clinical expertise to combine clinical and immunological findings. Here, we review classification criteria and current and future treatments with a mechanistic and evidence-based point of view.

2 Epidemiology

Lupus is a worldwide disease with a striking predilection for women of childbearing age. In women between the age of 15 and 44 years, the female to male ratio is up to 13:1 while it is only 2:1 in children and in the elderly [1–3]. While present across ethnicities, it is more prevalent in non-Caucasians. While prevalence in Europe and United States is higher in people of African descent, SLE is infrequent in Africa [4,5]. In the United States, it is more common in African-Americans, who also tend to have worse outcomes. In fact, African-American women are about 3 times more likely to have lupus and suffer greater mortality compared to Caucasian-Americans [6]. The Centers for Disease Control and Prevention report an estimated prevalence of about 322,000 cases of probable or definite SLE, higher in African Americans, American Indians and Alaska Natives [3,7–10].

3 Pathogenesis overview

The clinical onset of SLE requires an interaction of genetic predisposition, environmental precipitants, immunological and hormonal factors. In such a permissive environment, along with proinflammatory stimuli such as type 1 interferons and other cytokines, immune tolerance to self-antigens is lost [11]. Autoimmunity then follows driven by a complex interplay of defective clearance of apoptotic waste and immune complexes along with neutrophil extracellular traps, sensing of nucleic acids, disrupted lymphocyte biology, and interferon pathways [11].

The genetic susceptibility is suggested by the 11–50% monozygotic twin concordance and increased risk in families [12]. Many genes have been associated with a predisposition to develop lupus, typically encoding for immune components including HLA, IRF5, ITGAM, STAT4, BLK and CTLA4 among others [12,13].

Many environmental triggers have been implicated in lupus. Ultraviolet light (the most recognized), drugs/supplements (echinacea, trimethoprim/sulfamethoxazole) [14–16], smoking [17], infections [18,19] (Epstein-Barr virus in particular [20]), silica [21], mercury [22] and others [19,23,24]. Psychological stress has also been linked to a 50% increase risk of developing lupus [25,26].

In lupus, there is evidence for disruption of both the innate and adaptive arms of the immune system, connected in a feedback loop. T cells are defective and their aberration in lupus is complex [11,27,28]. They fail to produce enough IL-2 and there is a polarization toward Th17 over Tregs. There is an excess of double-negative T lymphocytes. T cells in SLE provide excessive help to B cells. There is evidence of an excess of autoreactive B cells but with overall B cell lymphopenia. The hyperactivation of the BLyS or BAFF pathway, a T cell independent B cell survival pathway, led to the development of a new biologic therapy, as described later.

In addition, the identification of a strong type 1 interferon “signature” in lupus recognized the pivotal role of the innate immune system [29–31]. Dendritic cells are central in the production of type 1 interferon and have a role in the clearance and sensing of nucleic acids and immune complexes, known autoantigens in lupus. In fact, endogenous and external nucleic acids are a major antigenic stimulus in lupus. Autoantibodies targeting nucleic acid-bound antigens are one of the hallmarks of the disease. The major source of such antigens come from apoptosis and neutrophils extracellular traps (NETs) [32–34]. Excess and impaired degradation of NETs are associated with lupus severity, lupus nephritis, anti-dsDNA antibodies and complement consumption [35,36].

Apoptosis is pivotal in the pathogenesis of lupus. Apoptotic cells such as UV-light exposed keratinocytes release blebs rich in autoantigens including Ro, La, and RNP [37,38]. In *in vivo* photosensitivity for example, immunocomplexes with endogenous nucleic acids can activate plasmacytoid dendritic cells via activation of TLR7 and 9 to produce conspicuous amounts of type 1 interferon [39,40]. These particles are physiologically coated by molecules such as C1q and IgM to facilitate phagocytosis and clearance in an “immunologically silent” and anti-inflammatory environment as mediated by dendritic cells [41,42]. Excessive non-cleared apoptotic waste is associated with inflammation and autoantibody production. For example, deficiency of C1q leads to early onset SLE in children [43].

The importance of this process is further substantiated by the role of DNAse1. DNAse1 is a nuclease involved in the processing of the nucleic acids exposed on apoptotic blebs. In the presence of DNAse1, apoptotic blebs tend to induce tolerance to self-DNA. When mutated or inhibited by anti-nucleic acids antibodies, the unprocessed nucleic acids trigger autoantibody production, type I interferon secretion, and provide a substrate for anti-dsDNA mediated immune complexes [35,44]. In fact, rare mutations in single genes involved in DNA damage repair, apoptosis, clearance of self-antigens, nucleic acid sensing, type 1 interferon production, and early complement components can lead to “monogenic lupus” and “interferonopathies” [45]. These observations highlighted the crucial role of the hypersensitivity to and inability to manage nucleic acids from dying cells as well as immunocomplexes, leading to the development of a “waste disposal” theory.

4 Diagnosis

The diagnosis of systemic lupus erythematosus is made based on a combination of typical clinical manifestations and positive serologies. Given the wide heterogeneity of clinical

manifestations, several sets of classification criteria have been developed over time for epidemiological and research purposes. However, some, such as the SLICC classification criteria, which are more sensitive, and therefore particularly useful in early diagnosis, can be useful as a diagnostic framework to confirm clinical judgment.

4.1 Classification criteria

The 1982 ACR criteria, revised in 1997, have been widely used for more than 3 decades [46,47]. The 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [48], were evidence-based, included a “stand alone” criterion of lupus nephritis, and required at least 1 clinical (acute cutaneous lupus, chronic cutaneous lupus, oral or nasal ulcers, synovitis, serositis, proteinuria or red blood cell casts, neurologic manifestations, hemolytic anemia, leukopenia or lymphopenia, and thrombocytopenia) and at least 1 immunologic criterion (ANA, anti-dsDNA, anti-Smith, anti-phospholipid antibodies, hypocomplementemia, and direct Coombs test) for a total of 4. The SLICC classification criteria are not limited to research and are widely used for diagnosis, as they are more sensitive and more comprehensive. The 2018 EULAR criteria, developed for research only, require an ANA of 1:80 or higher, and then weight lupus manifestations (for a score of 10) [49]. Direct comparison of the 3 sets of criteria using the SLICC validation cohort showed that they perform similarly with sensitivity and specificity of 89% and 90% for the EULAR, 83% and 96% for the ACR, and 97% and 84% for the SLICC criteria, respectively [50]. A systematic review and meta-analysis including 5236 patients and 1313 controls showed that the SLICC criteria have better sensitivity (94.6% vs 89.6%) and similar specificity (95.5% vs 98.1%) for adult SLE as compared to the 1997 ACR criteria [51].

4.2 Clinical diagnosis

This section describes key organ manifestations, including some recent developments, that are important in diagnosing lupus. Additional information and reviews of each clinical manifestation of lupus can be found elsewhere [52,53].

4.2.1 Cutaneous lupus—Skin involvement in SLE occurs in almost 90% of patients and includes lupus-specific manifestations such as acute cutaneous lupus, subacute cutaneous lupus, and chronic cutaneous lupus (discoid lupus, lupus profundus, chilblain lupus, and lupus tumidus. Non-lupus-specific manifestations include alopecia, vasculitis, livedo reticularis, periungual telangiectasias, and Raynaud’s phenomenon [54,55]. Most forms of cutaneous lupus share similar histological findings such as interface dermatitis with perivascular and periadnexial inflammation and may have immunoglobulin and complement deposition at the dermo-epidermal junction [55]. A biopsy is often key in the diagnosis of cutaneous lupus.

A key characteristic of cutaneous lupus erythematosus is the photosensitive distribution. Cutaneous lupus erythematosus must be differentiated from other more common photosensitive rashes such as polymorphous light eruption or rosacea. More than 50% of “photosensitive” biopsied rashes in SLE patients end up showing a non-lupus causation such as non-specific inflammatory reactions or polymorphous light eruption [56]. A true photosensitive rash in lupus is raised, delayed and long lasting. It typically occurs days after

ultraviolet light exposure [57,58], tends to last for more than 3 weeks [56], and may be associated with systemic symptoms such as arthralgia or fatigue [59].

Alopecia is common in SLE, but can have multiple causes. True lupus alopecia or “lupus hair” is reversible and characterized by shortening of the frontal hair which is irregular and with broken hairs at 5–25mm of length [60]. Discoid lupus can lead to permanent scarring lupus. Smoking is a risk factor for SLE [17], increases the risk of discoid lupus [61,62], increases ongoing cutaneous activity [63] and impairs the benefit of hydroxychloroquine [64].

4.2.2 Musculoskeletal involvement—Arthralgia and true synovitis are very common in SLE occurring in almost 90% [65]. It most typically presents as a symmetric polyarthritis involving the metacarpophalangeal, proximal interphalangeal, and knee joints [66]. Monoarthritis should prompt evaluation for alternative causes. Erosions are rare (unless sensitive imaging is used) and are associated with anti-cyclic citrullinated peptides antibodies [67]. Periarticular involvement including tendons and joint capsule is more common than previously understood (discovered by ultrasound and MRI) and can lead to reducible deformities known as Jaccoud’s arthropathy [68–70]. Articular ultrasound and magnetic resonance may help to differentiate active inflammatory disease from tenderness due to fibromyalgia and quantify the burden of disease [68–70].

Importantly, fibromyalgia, fibromyalgianess (the tendency to respond to illness and psychosocial stress with fatigue and widespread pain), and depression are common in lupus patients and associate with musculoskeletal pain; these do not track with disease activity and should not be misinterpreted as such [71,72].

4.2.3 Renal disease—Renal involvement is present in about 50% of patients with lupus with a predilection for certain ethnic groups such as African-Americans (70%) [73]. Early detection and treatment are paramount since lupus nephritis is a major cause of morbidity and mortality in SLE and delayed diagnosis is a risk factor for end-stage renal disease [74,75]. Renal disease is suspected when there is proteinuria [52,75]. However, lupus nephritis (class III, IV, and V) can be present in 25% of SLE patients without clinical signs of renal disease [76]. Urine protein levels above 500 mg/24h are associated with histopathological lupus nephritis and should prompt a renal biopsy [77]. Urine protein-to-creatinine ratio is a reliable measure of proteinuria in lupus nephritis, it is easier to routinely measure, and it is highly correlated with the 24h proteinuria [78]. In addition, clinical and serological (hypocomplementemia and elevation of anti-dsDNA antibodies) activity may further suggest lupus nephritis and is associated with higher risk histological features [77,79]. Anti-C1q antibodies are strongly associated with renal involvement in SLE, may predict flares, and their absence has a negative predictive value of nearly 100% [80–82].

Renal biopsy is essential to confirm the diagnosis, exclude alternative causes, evaluate for active inflammation versus irreversible damage, inform prognosis, and guide treatment. Lupus nephritis is classified based on clinicopathological correlations [83]. The Renal Pathology Society/International Society of Nephrology (or RPS/ISN) classification include 6 classes: minimal mesangial lupus nephritis, mesangial proliferative lupus nephritis, focal

lupus nephritis, diffuse lupus nephritis, membranous nephropathy, and advanced sclerosing lupus nephritis [83]. Additional renal diseases associated with lupus include lupus podocytopathy [84], tubulointerstitial nephritis, vascular disease (such as thrombotic microangiopathy, vasculitis, or atherosclerosis) [85], and collapsing glomerular sclerosis [86].

4.2.4 Central nervous system disease—A wide array of neuropsychiatric manifestations has been associated with SLE. However, only a few of them are more specific for SLE and are helpful for diagnosis [87,88]. These include seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, and acute confusional state [87,88]. Importantly, these require exclusion of other known causes.

In addition to clinical evaluation, magnetic resonance imaging (MRI) and cerebral spinal fluid analysis are important diagnostic tools. Central nervous system MRI is helpful to detect chronic microvascular changes, infarcts, hemorrhages, cortical atrophy, edema, abscesses, transverse and longitudinal myelitis [89,90]. Detection of long T2 of the gray matter (suggesting edema) or gadolinium enhancement in patients with active manifestations (seizures, psychosis, coma) may suggest activity, but generally, MRI cannot distinguish active from previous disease [89,91,92]. Identification of abnormal cerebrospinal fluid IgG and oligoclonal bands may help to identify active neuropsychiatric lupus [93]. Infection, metabolic-toxic and malignancy conditions always need to be considered in the differential diagnosis.

Up to 80% of SLE patients have cognitive impairment [94]. Formal psychometric testing and a psychiatric evaluation may be helpful to detect cognitive impairment and/or functional disorders [94,95]. Surprisingly, cognitive impairment (mild to moderate) is present in the majority of patient at the time of diagnosis, and does not worsen during follow up [96]. The most important correlate of cognitive impairment is depression [97].

5 Management

5.1 Principles

The goals of treatment in lupus are 1) maintain lowest degree of activity using immunomodulators, immunosuppression as appropriate and avoiding known triggers, 2) prevent organ damage from active lupus, 3) reduce comorbidities secondary to lupus and its treatment, especially accelerated atherosclerosis, the major cause of death, and 4) address fatigue and pain, which often are not associated with active lupus. Early initiation of treatment as well as partnership with the patient towards these shared goals is essential. This translates into avoidance of known triggers of flares, the need for sun protection, maximization of immunomodulators (hydroxychloroquine and vitamin D, including monitoring for adherence), avoidance of maintenance prednisone >6mg daily, and control of active disease with immunosuppression or biologics when required. Here, we review the rationale for current and future treatments.

5.2 Immunomodulators

Immunomodulators can favorably regulate the immune system in SLE without increasing the risk of infection or malignancy.

5.2.1 Hydroxychloroquine—Hydroxychloroquine pleiotropically modulates the immune response by inhibition of B cell receptor and TLR signaling as well as intracellular TLR-3 and-7 activation, fundamental in nucleic acid sensing [98–101]. It increases the lysosomal pH interfering with MHC-antigen binding, thus processing of autoantigens, as well as secretions of cytokines [102–104]. Hydroxychloroquine exerts an anti-type 1 interferon effect by interfering with the STING pathway [105].

Hydroxychloroquine is the cornerstone of medical therapy in lupus. It should be used in every patient unless there is a clear contraindication. It is the only medication shown to increase survival in lupus patients [106–109]. It has been shown to reduce lupus flares [110], prevent organ damage [111] including cardiovascular events [112], triple mycophenolate response in lupus nephritis [113], prevent seizures [114,115] and reduces the risk of developing neuropsychiatric lupus [116]. Hydroxychloroquine improves skin manifestations [117,118] and arthritis [119]. Hydroxychloroquine has a favorable effect on lipids [102,120–122], reduces insulin resistance [123] and the risk of thrombosis [124,125], and has a favorable effect on bone density [108,126].

Hydroxychloroquine is non immunosuppressive and does not increase the risk of infection or malignancy [127,128]. Retinal toxicity is a rare complication increasing after 20 years duration of treatment [129]. Retinal screening occurs at baseline, at 5 years, and then yearly [130]. Optical coherence tomography is the preferred screening test [36]. Hyperpigmentation can occur. Very rare complications include cardiomegaly and myopathy.

5.2.2 Vitamin D—Vitamin D should be supplemented in all SLE patients with insufficiency or deficiency, for its immunomodulatory and anti-fibrotic effects. Vitamin D immunomodulatory properties are mediated by the vitamin D3 receptor (VDR) in multiple immune cells lineages including monocytes, dendritic cells, and activated T cells as well as in the skin, vasculature and other tissues [131]. In vitro, vitamin D exerts an anti-inflammatory and anti-proliferative effect by promoting a Th1 (TNF-α, IL-2, IFN-γ) to Th2 (IL-4, IL-5, IL-10, GATA3) polarization as well as Th17 (IL12, IL23, IL-6, 17) to Treg (IL-10, TGF-β, FoxP3, CTLA4) state [132]. It affects the development and function of NKT cells [133].

In addition, vitamin D may act as an anti-fibrotic agent. Vitamin D deficiency is associated with increased risk of multiorgan fibrosis including, among others, the kidneys and the lungs [134]. Importantly, patients with lupus nephritis refractory to mycophenolate have increased expression of profibrotic pathways in the affected kidneys [135] suggesting that renal tissue could be rescued by targeting such pathways. Vitamin D supplementation prevented fibrosis in animal models and inhibits pro-fibrotic pathways mediated by TGF-beta and Ras [134,136].

Vitamin D deficiency is common in patients with SLE [137]. Some VDR polymorphisms are associated with lower serum vitamin D levels and have been associated with SLE [138]. In patients with lupus, vitamin D deficiency correlates with increased disease activity and fatigue [139,140] as well as an increased risk for thrombosis, including from antiphospholipid antibodies [141,142]. Importantly, supplementation of vitamin D is associated with reduction of proteinuria, higher complement levels, and improvement in global disease activity in SLE as demonstrated in an observational cohort and in a randomized controlled study [143,144]. Supplementation should be aimed to a 25(OH) vitamin D level of 40 ng/ml [143,144]. Vitamin D supplementation is safe [143] and should be continued indefinitely. Vitamin D levels should be monitored periodically to assess adequate absorption and dosing and adherence.

5.2.3 Dehydroeipandrosterone (DHEA)—DHEA is an adrenal hormone regulated by ACTH [145]. It is an important precursor of both estrogens and androgens via peripheral conversion [146]. Women with lupus tend to have lower levels of androgens, higher estradiol, lower DHEA and DHEA-S (its metabolite), independently of corticosteroid use [147,148]. In addition, DHEA supplementation has been associated with regulation of proinflammatory cytokines (IL-2, IL-1, IL-6, TNF-a) and may reduce antibody production in mice [149–152].

Many of the several randomized clinical trials in women with SLE showed a modest improvement in disease activity along with improvement in cytokine profile and bone density [153,154]. DHEA should not be used in postmenopausal women since it may increase the risk of hormone sensitive malignancies. There is no evidence to support DHEA use in men.

5.3 Corticosteroids

Corticosteroids affect all components of the immune system [155]. High dose or “pulsed” corticosteroids are important to rapidly ablate the autoimmune response in life or organ threatening manifestations such as some cases of nephritis, vasculitis, central nervous system lupus, myocarditis, or alveolitis, among others. In lupus nephritis for example, pulsed therapy (250–1000mg IV daily for 3 days) was previously recommended along with cyclophosphamide or mycophenolate for induction, but there is no consensus on an oral maintenance regimen [156,157]. The “rituxilup” protocol showed that lupus nephritis remission can be induced without any oral corticosteroids using rituximab and mycophenolate suggesting that corticosteroids might not be necessary to control even severe lupus manifestations [158]. In the recent voclosporin phase 2 clinical trial, only 25 mg of prednisone was used [159]. Importantly, any of the studied immunosuppressants agents (cyclophosphamide, azathioprine, mycophenolate, tacrolimus) is better than corticosteroids alone to prevent end stage renal disease [160].

Oral corticosteroids should be avoided as much as possible. In lupus patients, 80% of organ damage after diagnosis is directly or indirectly attributable to prednisone [161]. Doses of even 10 to 20 mgs daily increase the risk of cardiovascular events [162] and any dose above

6 mg increases later organ damage by 50% [163]. Even low doses, over time, increase cataracts, osteoporosis, fractures and coronary artery disease [164].

Intramuscular triamcinolone, or a brief 1-week methylprednisolone dose pack, is effective for management of most mild to moderate flares. Results from the FLOAT trial showed that a single intramuscular triamcinolone 100 mg injection is a faster acting and effective alternative to oral maintenance corticosteroids [165]. As it is released slowly, its effect lasts for about 1 month and has equipotency of approximately 2 mg of prednisone daily.

5.4 Cytotoxic-immunosuppressants

5.4.1 Cyclophosphamide—Cyclophosphamide is a highly toxic alkylating agent that depletes T and B cells and suppresses antibody production [166]. It was more widely used in the past for the induction and maintenance of lupus nephritis [167,168] and other severe lupus manifestations such as central nervous system lupus [169]. However, it has now been largely replaced by less toxic immunosuppressive medications such as mycophenolate, calcineurin inhibitors, and azathioprine for nephritis and rituximab for severe central nervous system lupus [170,171]. Cyclophosphamide is associated with premature ovarian failure, hemorrhagic cystitis, increased risk of bladder and other malignancies, and leukopenia along with an increased risk of infections [172].

5.4.2 Azathioprine—Azathioprine is a purine analogue. It is converted *in vivo* to 6-mercaptopurine followed by thioinosinic acid and 6-thioguanine which are incorporated into DNA and RNA, inhibiting their synthesis. Besides its antimetabolite role, azathioprine may have a tolerogenic effect by inhibiting CD28-mediated signal 2 in T cells [173].

Azathioprine has been commonly used in renal and extrarenal lupus since the late 1960s. In two small randomized studies, azathioprine compared to corticosteroids alone was shown to reduce mortality, rate of flares and corticosteroid use, including patients with severe renal or central nervous system disease [174,175]. In the following decades, its use in induction in lupus nephritis waned given its inferiority to cyclophosphamide [176,177]. Azathioprine was inferior to mycophenolate in the ALMS trials and equal in the MAINTAIN trial [178,179].

In extrarenal lupus, azathioprine is widely used as a corticosteroid sparing agent [180]. However, a recent non-blinded randomized controlled study showed that mycophenolate was superior to azathioprine to control disease activity and prevent flares (renal and extrarenal) while maintaining a similar side effect profile [181].

Azathioprine remains an excellent choice to control renal and extrarenal disease during pregnancy as the metabolite 6-MMP is not generated in the fetus [182,183].

5.4.3 Methotrexate—Methotrexate is an antimetabolite the interferes with DNA synthesis, repair, and replication by irreversibly binding to dihydrofolate reductase, thus reducing purine synthesis. However, the mechanism of its anti-inflammatory effects goes beyond arresting the cell cycle by folate depletion and is not completely understood [184]. For instance, co-administration of folate does not impair its efficacy, while mitigating side effects. Low-dose methotrexate has pleiotropic effects involving increased anti-

inflammatory adenosine signaling, apoptosis of activated lymphocytes, reduction of circulating pro-inflammatory T-cells, reduction of adhesion molecules on endothelial and synovial cells, reactive oxygen species, and others [184].

In lupus, methotrexate has been used since the 1960s [185]. Combined evidence from 3 small randomized trials and several observational studies showed that methotrexate reduced disease activity, was corticosteroid sparing, had efficacy for joint and skin disease, and ameliorated anti-dsDNA and complement levels [186]. Methotrexate showed a modest steroid sparing activity in a randomized controlled trial [187].

5.4.4 Mycophenolate—Mycophenolate preferentially depletes guanoside nucleotides in T and B cells inhibiting proliferation. It suppresses lymphocyte and monocyte recruitment to inflamed tissue. It inhibits inducible nitric oxide synthase which may curtail nitric oxide oxidative tissue damage mediated by macrophages [188].

Mycophenolate is effective for induction and maintenance of lupus nephritis [178,179,189–191]. The ALMS trial (n=140) showed that 22.5% of patients treated with mycophenolate achieved complete renal remission at 24 weeks compared to 5.8% in the cyclophosphamide group [190]. The larger ALMS lupus nephritis induction trial showed similar efficacy of mycophenolate compared to cyclophosphamide [191]. Mycophenolate had a better safety profile. This was confirmed by a recent Cochrane systematic review, although with low certainty evidence [192]. This review also confirmed that mycophenolate is superior to azathioprine in preventing nephritis relapses. Mycophenolate is also effective in extrarenal lupus in all the analyzed domains in multiple case series and in a post-hoc analysis of the ALMS trial [193,194].

5.4.5 Calcineurin inhibitors—Calcineurin inhibitors target T cells by blocking the inhibition of calcineurin [195]. This prevents translocation of transcription factors such as nuclear factor of activated T-cells (NFAT) resulting in T cells inhibition with reduction of IL-1b, IFN-γ, IL-6 and IL-10. B cell activation is also impaired along with class switching and immunoglobulin production. Furthermore, calcineurin inhibitors affect the kidneys directly by stabilizing podocytes, reducing mesangial proliferation, and improving proteinuria [196–198].

Calcineurin inhibitors are commonly used to prevent transplant rejection. In lupus, tacrolimus has been used, alone or in combination with mycophenolate, more extensively than cyclosporine given its better side effects profile [199]. However, both have significant variability in plasma concentration and require monitoring.

Multiple small RCTs showed that lupus nephritis induction with calcineurin inhibitors (cyclosporine or tacrolimus) is as effective as cyclophosphamide or mycophenolate [200–203]. A recent metanalysis suggested a possible superiority of tacrolimus over cyclophosphamide [204]. A larger trial comparing mycophenolate vs tacrolimus in 150 Chinese patients with active class III/IV showed similar complete response rates at 6 months (59% vs 62%, respectively) and side effects [205].

Combination of calcineurin inhibitors and mycophenolate is used to prevent graft rejection and is also effective in refractory lupus nephritis in Caucasian and African American patients [206–208]. In a large RCT, 368 Chinese patients with class III/IV/V lupus nephritis were randomized to receive a combination of tacrolimus (4 mg/day) and low dose mycophenolate (1 g/day) ("multitarget") or monthly IV cyclophosphamide (0.5–1 g/m2) [209]. After 6 months, complete remission was achieved in 45.9% vs 25.6%, and overall response in 83.5% vs 63% in the multitarget and cyclophosphamide, respectively. More patients withdrew from the multitarget arm, mostly due to pneumonias and zoster reactivation [209].

Calcineurin inhibitors have also been proven effective for maintenance therapy of lupus nephritis [210,211], as well as for pure membranous lupus nephritis with a significant antiproteinuric effect [205,212–215]. They are recommended by EULAR [157].

Voclosporin is a new calcineurin inhibitor. It has greater pharmacological potency, faster elimination and less variability in blood concentration. It is non-inferior to tacrolimus in preventing kidney transplant rejection [216]. The AURA phase IIb study randomized 265 patients with active lupus nephritis to receive voclosporin or placebo in addition to mycophenolate and corticosteroids [159,217]. Both voclosporin doses showed higher complete remission rate than mycophenolate alone at 24 and 48 weeks (48 weeks complete remission 40%, 49%, and 24% in the high dose, low dose, and mycophenolate alone arm, respectively). Glomerular filtration rate decreased with voclosporin. There was an imbalance of death in the low dose voclosporin arm. A phase III trial (AURORA) is ongoing.

5.5 Biologics and small molecules

5.5.1 Available

5.5.1.1 Rituximab: Autoantibodies and immune complex formation are an immunological hallmark of lupus. B cells have been targeted in SLE for years with immunosuppressants such as cyclophosphamide and mycophenolate. Targeted therapies toward B cells that avoid broad immunosuppression are the goal.

Rituximab is an anti-CD20 monoclonal antibody that leads to peripheral B cell depletion. Several observational studies showed benefit in renal and non-renal lupus [218,219]. Two large randomized placebo-controlled trials in renal and non-renal lupus failed to meet their primary outcomes. In the EXPLORER non renal trial [220], the primary (proportion of patients achieving complete or partial remission based on BILAG score) and secondary endpoints were not met. B-cell depletion was obtained in about 90% of treated patients. Rituximab did reduce anti-dsDNA titers and improved C3 and C4 levels.

In the LUNAR renal trial [221], 144 patients with class III or IV lupus nephritis were randomized to receive rituximab (1,000 mg on day 1, 15, 168, and 182) or placebo in addition to mycophenolate and corticosteroids. The rituximab group failed to achieve the primary outcome defined as better overall (complete and partial) renal response compared to mycophenolate alone at 52 weeks (57% vs 46%, $p = 0.18$). Further analysis showed that rituximab did reduce proteinuria better than mycophenolate alone at 18 months and reduced the need for rescue cyclophosphamide (8/72 in the placebo group vs 0/72 for rituximab).

The disappointing results led to the consideration of the issue of reconstitution of B cells after rituximab [222]. The surge of BAFF upon depletion of B cells with rituximab may contribute to the lack of sustained response to rituximab [223–225]. This provided the rationale for SynBioSe, a proof of concept phase 2A trial of rituximab followed by belimumab in patients with refractory severe lupus nephritis [226]. Eleven out of 16 patients showed a renal response, 5 with complete response. The renal response was paralleled by amelioration of immune-complex mediated NETs formation. In the CALIBRATE trial, patients with refractory lupus nephritis were treated with rituximab, cyclophosphamide and corticosteroids followed by either belimumab or placebo. This did not show a benefit of belimumab, with 24 week renal responses of 24% vs 23%. [227].

Evidence for the efficacy of rituximab comes from “rituxilup”, an oral corticosteroid-avoidance protocol to treat lupus nephritis with mycophenolate and rituximab. In this prospective observational single-center cohort study, partial or complete remission was achieved in 45 of 50 patients by a median time of 37 weeks [158].

5.5.1.2 Belimumab: B cells maturation, Ig-class switching, and antibody production are most potently driven by antigen specific T cells. Since T cells tolerance is much more strictly regulated, such T cell dependence should ensure that autoreactive naïve B cells that escaped central tolerance will be eliminated by lack of stimulation. However, T cell-independent pathways such as B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) may bypass T cells in the selection of autoreactive B cells. BAFF exists in a soluble and membrane bound form and is produced by antigen presenting cells (dendritic cells, B-cells, monocyte/macrophages, plasmacytoid dendritic cells), neutrophils, activated T cells and endothelial cells [228]. BAFF provides essential activation and survival signals via NFkB and MAP-K pathways to B cells as mediated by 3 receptors: BAFFR, TACI and BCMA. BAFFR ligation provides the strongest signal while TACI and BCMA also bind to APRIL [229]. Importantly, patients with lupus have higher circulating BAFF and APRIL levels and the BAFF level is predictive of flares [230]. BAFF-transgenic mice have a lupus-like phenotype independent of T cells [231].

Two large phase 3 RCT, BLISS-52 and BLISS-76, assessed the SLE responder index at 52 weeks in patients with non-renal lupus [232,233]. In both trials, there was a higher response rate with the higher dose of belimumab (10 mg/kg) compared to standard of care (BLISS-52: n=867, 58% vs 44%, p=0.006; BLISS-76: n=819, 43.2% vs 33.5%, p=0.017). Belimumab also significantly reduced the number of flares. In addition, belimumab normalized anti-dsDNA in up to 17–25% (placebo 6–8%) and normalized C3 in 34–44% (vs 14–21%) and C4 in 43–46% (vs 17–19%). Belimumab decreased circulating B cells and CD20+/CD27^{bright} short lived plasma cells were decreased by >50% and up to 43%, respectively. Pooled data analysis of both trials showed that combined hypocomplementemia and anti-dsDNA positivity was the best predictor of response to belimumab [234]. Based on these results, belimumab became the first new drug in the last five decades to be approved by the EMA and FDA (and later by NICE) for the treatment of active non-renal lupus despite standard therapy.

5.5.2 Currently studied

5.5.2.1 Anifrolumab: Type 1 interferon signaling is mediated by the type I IFN-α/β/ω receptor (IFNAR). Anifrolumab is a monoclonal antibody blocking IFNAR. In a phase 2b trial, 305 lupus patients were randomized to receive placebo or one of two dosages of anifrolumab [235]. At 24 weeks, 34% and 29% of patients receiving anifrolumab (300mg and 1000mg every 4 weeks, respectively), while only 17.6% in the placebo group, achieved the primary outcome of SRI-4 response with sustained reduction of oral corticosteroids. The effect was greater in patients with the interferon signature at baseline. Both skin and joint disease showed a favorable response. In addition, anifrolumab was associated with decreased anti-dsDNA titers and higher C3 levels. There was a mild increased risk of viral infections, including influenza and herpes zoster. However, the first phase III trial (TULIP 1) did not reach its primary end point of decreasing the SRI-4 [236]. TULIP 2 is currently under way.

5.5.2.2 Ustekinumab: There is increased Th17 activity in lupus. Serum IL-17 and IL-23 levels are higher in SLE and correlate with disease activity [28]. IL-17-producing cells are present in biopsies from lupus nephritis [28]. Double negative T cells are also a source of IL-17. STAT3, which is downstream to IL-23 stimulation, is upregulated in lupus [237], and promotes IL-17 production as well as differentiation toward Th17 and Tfh [238]. Tfh are expanded in SLE and have been implicated in the overstimulation of B cells [239]. IL-23 promotes the development of double negative T cells [240] and impairs the production of IL-2 suggesting a possible indirect effect on the production of Tregs [241].

The IL-23/Th17 axis can be disrupted by ustekinumab, a monoclonal antibody blocking IL12 and IL-23 currently approved to treat psoriasis, psoriatic arthritis and inflammatory bowel disease. In a phase 2 trial, 102 patients with SLE were randomized (3:2) to ustekinumab vs placebo. At 24 weeks, 60% of ustekinumab-treated patients achieved the primary endpoint, SLE responder index-4 (SRI-4) compared to 31% in the standard of care group (p=0.0046). Subgroup analysis showed significant improvement in skin and joint scores. Ustekinumab improved C3 and reduced anti-dsDNA levels [242].

5.5.2.3 Baricitinib: The Janus kinases (JAKs) are a family of tyrosine kinases mediating intracellular signaling of several cytokines via the JAK-STAT pathway. Inhibition of a single JAK may lead to blocking the downstream effect of several cytokines at the time. However, this is a redundant system in which a group of cytokines may signal through different JAKs and different JAKs mediate signaling from different groups. At present, baricitinib and tofacitinib are FDA approved for the treatment of rheumatoid arthritis. Baricitinib is a reversible inhibitor of JAK1 and JAK 2. These mediate signaling for type 1 interferons, IFN-γ, IL-6, IL-12, and IL-23 among others [243]. An international, multicenter, double-blind, placebo-controlled phase 2 trial assessed the efficacy of baricitinib in patients with SLE. The primary outcome was the proportion of patients achieving resolution of rash or arthritis at 24 weeks, defined by SLEDAI-2K [244]. Three-hundred and fourteen patients with inadequate control despite standard of care were included. The primary outcome was achieved in a statistically significant higher proportion of patients treated with baricitinib 4 mg daily, but not 2 mg daily, as compared to placebo (67% vs 58% vs 53%, respectively). Most of the

results were driven by the baricitinib effect on arthritis as no significant difference was noted on skin scores. The frequency of flares was also lower in the 4 mg group compared to placebo (33% vs 51%). There were more serious infections in the 4 mg arm (6%) compared to the 2 mg (2%) and placebo (1%). There was 1 deep venous thrombosis (1%) detected in the 4 mg arm.

5.5.2.4 Atacicept: Atacicept is a TACI-Ig fusion protein that inhibits B cells by dual inhibition of APRIL and BLyS. In a phase 1b trial, atacicept showed a dose dependent reduction in circulating B cells and immunoglobulins [245]. In the ADDRESS II, a phase 2b trial, 306 patients were randomized to receive weekly subcutaneous atacicept (75mg or 150mg) or placebo [246]. Atacicept was associated with a trend toward better SRI-4 response at 4 weeks compared to placebo, especially in individuals with high disease activity, serologically active disease, or both. For example, in the serologically active group, 62% of patients treated with atacicept achieved SRI-4 at 24 weeks compared to 24% in the placebo arm [246].

5.6 Lifestyle

Some of lupus management is non-pharmacological [247]. Patients should avoid sun exposure using protective garments and sunscreen of at least SPF 50 (as demonstrated in a randomized clinical trial [248]).

Fibromyalgia and “fibromyalgia-ness” (tendency to respond to illness and psychosocial stress with fatigue, general increase in symptoms, and widespread pain) is increased in SLE [249,250]. Regular exercise, stretching and can help to improve fatigue, cognitive dysfunction, and pain from fibromyalgia [251–253].

5.7 Prevention of comorbidities

Lupus confers a 2.4-fold increase in all-cause mortality. The number one cause of death in lupus is cardiovascular events, followed by infections, and finally by renal and respiratory complications of lupus [74].

The risk of cardiovascular events is increased 2.66 fold [162]. Therefore, aggressive management of traditional (smoking, obesity, diabetes mellitus, hypertension, dyslipidemia) and lupus (lupus activity, antiphospholipid antibodies, homocysteinemia, excessive corticosteroid use) modifiable cardiovascular risk factors is paramount to prevent early death [254].

Homocysteinemia is present in 15% of patients [255] and has an independent association with cardiovascular risk [256–258], renal injury and fibrosis [259,260], and is associated with higher prevalence of myocardial infarction and thrombosis in patients with antiphospholipid antibodies [261]. Hyperhomocysteinemia is an independent risk factor for cardiovascular disease in patients with lupus [255].

Infections are common in lupus, particularly from encapsulated bacteria [262]. Typical organisms are the most common causal agents but opportunistic bacterial, mycobacterial, protozoal, fungal and viral infection are also increased [263]. Pneumonia, especially from

Streptococcus pneumoniae, is common in lupus and is associated with excess mortality [74,263]. In addition to the local immunization schedule, pneumococcal and influenza vaccination should be followed.

Osteoporosis and fragility fractures are higher in lupus [264–266]. Notably, fracture risk calculators may underestimate in lupus [267]. Optimal bone health should be pursued recommending smoking cessation, optimal vitamin D levels, adequate dietary calcium intake (rather than supplementation [268]), weight bearing exercise, avoidance of corticosteroids, bone density screening according to risk and treatment with DHEA (never in men) and bisphosphonate as appropriate [154,267].

6 Future perspectives and personalized medicine

The more granular understanding of the molecular basis of lupus pathogenesis has led to several new promising treatments that are undergoing late phase clinical testing. These recent phase 2 trials underlined how targeting a specific pathway may elicit dramatically different responses in patient subgroups. Precise characterization of disease phenotypes based on molecular and clinical features is crucial to design personalized treatment. The Accelerated Medicine Partnership (AMP), for example, is an ongoing effort to identify the molecular pathways, at the single cell level, involved in lupus nephritis [269]. This may help to redefine the way we classify SLE and lupus nephritis and identify precise predictors of treatment response. We expect that the understanding of the heterogeneity of autoimmunity in lupus will lead to more effective and less toxic regimens in the future.

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Highlights

- Classification criteria are a helpful diagnostic framework to confirm clinical judgement.
- Hydroxychloroquine is the cornerstone of medical therapy in lupus.
- Immunosuppression and targeted therapies are paramount for renal and severe extra-renal lupus manifestations.
- New therapies targeting the Th17, BAFF, JAK/STAT, and calcineurin pathways showed positive phase 2b trial results.