Chapter

Novel Therapeutic Interventions in Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease. It is characterized by a variable clinical course ranging from mild to fatal disease. It can affect the kidneys. The aim of treatment in SLE is the prevention of flares and the prevention of accumulation of damage to the main organs affected as well as the prevention of drug side effects. The cornerstone of SLE treatment is hydroxychloroquine. Corticosteroids are used both as induction treatment in disease flares as well as in small doses as maintenance treatment. Immunosuppressants, such as azathioprine, methotrexate and mycophenolate mofetil are used as steroid sparing agents. Calcineurin inhibitors, namely tacrolimus and cyclosporin A may also be used as immunosuppressants and steroid sparing agents. Pulse methylprednisolone, along with mycophenolate mofetil and cyclophosphamide are used as induction treatment in lupus nephritis. Rituximab, an anti-CD20 biologic agent may be used in non-renal SLE. In patients insufficiently controlled with hydroxychloroquine, low dose prednisone and/or immunosuppressive agents, belimumab may be used with beneficial effects in non-renal disease and lupus nephritis.

Keywords: systemic lupus erythematosus, treatment, hydroxychloroquine, corticosteroids, mycophenolate mofetil, rituximab, belimumab

1. Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease affecting many organ systems. It has a variable course, ranging from a mild course to severe fatal disease. It affects mainly women in the reproductive age. Women of African or Asian origin suffer frequently and present with more severe disease. The treatment of SLE is in the focus of scientific interest as new immune modulating agents have entered the management of the disease.

The therapeutic management of the disease depends mainly on antimalarial agents, namely hydroxychloroquine, corticosteroids, immunosuppressive agents and biologic drugs (**Figures 1** and **2**). The use of hydroxychloroquine is established in SLE. Similarly, the use of corticosteroids has been in the mainstream of lupus treatment for many years. Their use is hindered by their adverse effects, which may occur even with small doses. Immunosuppressive agents such as azathioprine and methotrexate have been used as steroid sparing agents. The use of mycophenolate mofetil (MMF) is also in the mainstream treatment of severe SLE cases or lupus nephritis. Rituximab, an antiCD20 antibody targeting B lymphocytes has also been

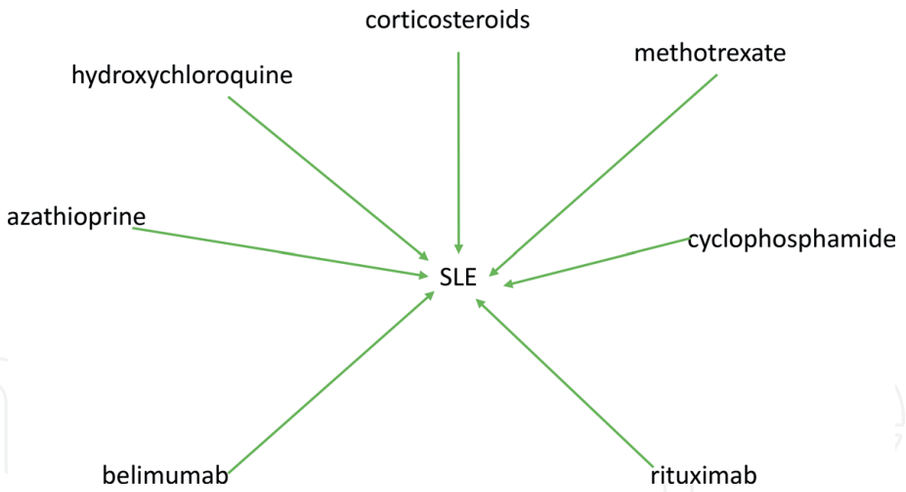

Figure 1.
Agents involved in systemic lupus erythematosus treatment.

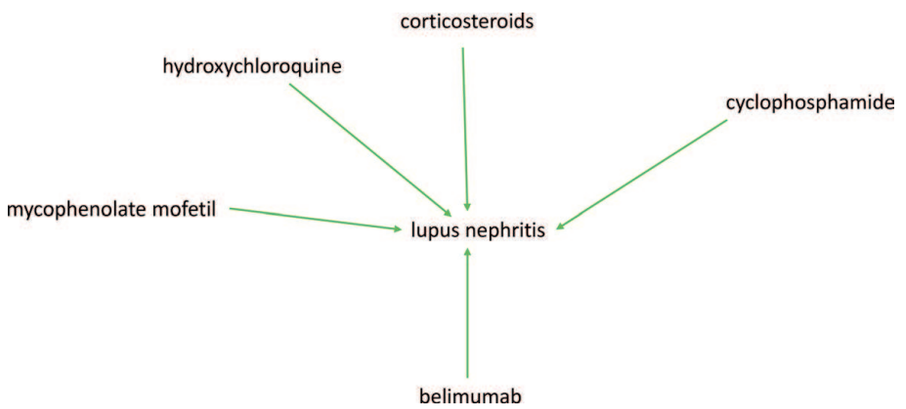

Figure 2.
Agents contributing to the treatment of lupus nephritis.

applied in the treatment of severe SLE cases. Recently, the use of belimumab has been introduced in the treatment of SLE and is indicated in patients with non-renal disease and renal disease not responsive to standard treatment. Although, recent advances in treatment have improved prognosis and life expectancy in lupus patients, much progress remains to be achieved. In the present chapter, the use of various treatment modalities for SLE will be discussed. Additionally, the use of supplementary drugs will be reviewed.

2. Systemic lupus erythematosus treatment

2.1 Antimalarials

Antimalarials have been used for many years in the treatment of rheumatic diseases [1, 2]. Historically, antimalarials had been observed to ameliorate rheumatic symptoms in soldiers taking these drugs during World War II for the prevention of malaria [3]. Clinical application of hydroxychloroquine and chloroquine in the treatment of rheumatic diseases has been widely reported. The use of hydroxychloroquine in the treatment of SLE has been well established [4, 5]. It has been used in both discoid lupus and SLE [6]. Chloroquine and hydroxychloroquine increase pH within intracellular vacuoles and modify processes such as protein degradation by acidic hydrolases in the lysosome, organization of macromolecules in the

endosomes, and post-translation modification of proteins in the Golgi apparatus. The antirheumatic properties of antimalarials is a consequence of their interference with antigen processing in antigen-presenting cells. For the digestion of antigenic proteins and for the peptides to assemble with the chains of the MHC class II proteins it is necessary to have acidic cytoplasmic compartments. Antimalarials increase the pH thereby diminishing the formation of peptide-MHC protein complexes which are required to stimulate CD4+ T cells and down-regulating the immune response against autoantigenic peptides [7, 8]. It also blocks Toll-like receptors on dendritic cells [9]. A review of controlled trials on the clinical efficacy and safety of antimalarials showed that adequate evidence exist for these drugs, in particular hydroxychloroquine in preventing lupus flares, increasing long term survival of patients and lupus activity in pregnant women without proven teratogenicity [10]. Moderate evidence exists for the prevention of irreversible organ damage, prevention of bone destruction and prevention of thrombosis. Weaker evidence exists for the reduction in severe lupus activity, lipid levels and subclinical atherosclerosis [11]. Hydroxychloroquine has been shown to improve glucose metabolism [12]. The toxicity of antimalarials is mild, infrequent and it is usually reversible. When given attention to dosage hydroxychloroquine has a safer profile. Ruiz-Irastorza et al recommended that hydroxychloroquine should be given to all patients with lupus during the full course of the disease [13]. They have described hydroxychloroquine as being the cornerstone of lupus treatment [13]. There have been very few efforts on discontinuation of the drug due to its proven efficacy and the few and mild side effects. Hydroxychloroquine has multiple beneficial effects in SLE. It reduces lipid levels, thereby inhibiting atherosclerosis [14, 15]. Hydroxychloroquine has multiple effects on cholesterol metabolism, as it inhibits cholesterol biosynthesis, inihibits lysosomal hydrolysis of cholesteryl ester and stimulates the capacity of LDL receptor and the activity of HMG-CoA reductase [16]. Hydroxychloroquine protects lupus patients from thrombosis, as it has known antithrombotic action. It reduces red blood sludging, blood viscosity, platelet aggregation and protects the annexin V "shield" from disruption by antiphospholipid antibodies [17]. Additionally, it reduces glucose levels via multiple mechanisms [18].

2.2 Corticosteroids

Corticosteroids have been used at large bolus doses as induction treatment as well as at small doses as maintenance treatment in patients with SLE [19] (**Figure 1**). They reduce disease activity as well as disease burden accrual on different organ systems [20]. Corticosteroids have potent immunomodulatory properties [21]. They are known to modulate all aspects of immune response and have strong immunosuppressive and anti-inflammatory properties [22, 23]. Their effects on the immune system are known to be mediated mainly by their trans repression mode of action, namely by their ability to reduce the expression of inflammatory transcription factors [24]. As corticosteroids are characterized by many severe and less severe side effects such as propensity to infections [25, 26], blood glucose elevation [27] and osteoporosis [28], different immunomodulating agents have been applied in patients with SLE as corticosteroid sparing agents.

Methylprednisolone pulse therapy is used for the treatment of severe manifestations of SLE. Intravenous pulses of prednisolone rapidly immunosuppress patients with organ and/or life-threatening manifestations of SLE [29, 30]. The gold standard is 1 g/day for 3-5 days [31]. However, this treatment schedule may be associated with significant infectious complications and lower doses may be useful as well. In particular, it has been shown that a lower dose pulse methylprednisolone treatment schedule involving ≤1500 mg/3 days may have the same beneficial effects

and fewer adverse effects, in particular severe infections [32]. An intensive treatment schedule of rituximab, cyclophosphamide and intravenous pulses of methylprednisolone has been applied with excellent results in patients with SLE and severe organ manifestations including nephritis [33]. Patients improved significantly and long-term immunosuppression other than prednisone 5 mg/day was avoided.

Corticosteroids in the form of prednisone daily as maintenance treatment for SLE patients has been applied for years. New data show that introducing lower initial doses of prednisone (<15 mg/day) and thereafter tapering to low doses of prednisone (5 mg/day or even lower) has been shown to be effective in SLE [34–36]. Mild flares can be managed with transient increases of prednisone up to 15 mg/day with rapid reduction. In moderate severe flares the use of pulse methylprednisolone 125 mg, 250 mg or 500 mg/day for three consecutive days is much more effective and less toxic than increasing oral prednisone to 0.5-1 mg/kg/day [32]. Rapid reduction from doses up to 30 mg/day prednisone should be performed to 5-2.5 mg/day within few weeks. Immunosuppressive therapy should be started early in severe forms of the disease and when prednisone cannot be reduced to 5 mg/day or less.

2.3 Immunosuppressants

2.3.1 Azathioprine

Azathioprine is a purine analogue. It inhibits DNA synthesis by acting on proliferating cells [37]. It acts on the DNA [38]. Azathioprine is metabolized to 6-mercaptopurine through reduction by glutathione and other sulfhydryl-containing compounds and then enzymatically converted into 6-thiouric acid, 6-methyl-mercaptopurine, and 6-thioguanine [38]. Ultimately, azathioprine is incorporated into replicating DNA and can block the de novo pathway of purine synthesis. It is this action that is thought to contribute to its relative specificity to lymphocytes due to lack of a salvage pathway. The inhibition of purine synthesis, leads to less DNA and RNA available for the synthesis of white blood cells, including cells of the immune system. Actively replicating cells, such as T cells and B cells of the immune system, which actively synthesize purine to make new DNA are strongly affected [39, 40]. Thus, immunosuppression ensues. It has been used successfully in SLE as steroid sparing agent and in cases of lupus flares. It can be used safely during pregnancy [41]. It can be used as maintenance treatment in lupus nephritis [42].

2.3.2 Methotrexate

If the disease is not controlled with up to 5 mg prednisone methotrexate can be used as an immunosuppressant and steroid sparing agent [43, 44]. Methotrexate exerts anti-inflammatory actions through some well-known and other less well-known mechanisms [45, 46]. It inhibits dihydrofolate reductase thus diminishing the de novo synthesis of purines and pyrimidines by preventing the regeneration from dihydrofolate of tetrahydrofolate. Tetrahydrofolate is essential for the generation of folate cofactors required for purine and pyrimidine synthesis [47]. The reduction in the levels of methyl donors, such as tetrahydrofolate and methyl tetrahydrofolate, by the inhibition of dihydrofolate reductase results in the inhibition of the generation of lymphotoxin polyamines through methionine and S-adenosylmethionine. The inhibition of amino-imidazole-carboxamido-ribonucleotide transformylase results in an increase in intracellular amino-imidazole-carboxamido-ribonucleotide levels. This increase has potent inhibitory effects on AMP deaminase and adenosine deaminase. Thus, adenosine is accumulated. Adenosine confers anti-inflammatory effects [48, 49]. Methotrexate has favorable effects on

the joints and the skin [50]. It is teratogenic, therefore if pregnancy is contemplated it should be withdrawn before conception [51].

2.3.3 Mycophenolate mofetil

Mycophenolate mofetil (MMF) has been used for many years in the treatment of SLE. It is a potent immunosuppressing agent with efficacy in lupus nephritis [52] (**Figure 2**) and non-renal lupus [53]. It is particularly indicated in patients with lupus nephritis [54]. MMF is an inhibitor of purine synthesis and it acts to inhibit lymphocyte proliferation and nitric oxide production by activated macrophages [55]. MMF is a prodrug of mycophenolic acid. Mycophenolic acid is an inhibitor of inosine-5'-monophosphate dehydrogenase [55], it depletes guanosine nucleotides preferentially in T and B lymphocytes and inhibits their proliferation, thereby suppressing cell-mediated immune responses and antibody formation, it inhibits the glycosylation and expression of adhesion molecules, and the recruitment of lymphocytes and monocytes into sites of inflammation, it depletes tetrahydrobiopterin and decreases the production of nitric oxide by inducible NO synthase without affecting the activity of constitutive NO synthases. By these mechanisms MMF exerts anti-inflammatory activity [55]. MMF quickly and persistently reduces numbers of activated B cells and levels of free immunoglobulin light chains [56]. Careful studies in lupus nephritis have established the equivalence of MMF to intravenous (I.V.) cyclophosphamide and its equivalence or superiority to azathioprine in the maintenance phase of treatment [Aspreva Lupus Management Study (ALMS), (MAINTAIN) trial] [57–61]. MMF is effective in non-renal lupus as well. In a systematic review of 20 case series and open-label trials MMF was shown to benefit patients with hematological manifestations and refractory dermatological involvement [62]. It has also been shown to improve lupus arthritis. MMF has side effects including gastrointestinal symptoms, bone marrow suppression, infection risk and long-term risk of cancer from immunosuppression. It appears to be less toxic than cyclophosphamide. Cases of drug sensitivity to MMF have been reported among an Asian subgroup of patients when combined with high-dose corticosteroids [62–64]. By contrast, MMF appears to be more effective in preventing renal flares in high-risk populations such as African Americans [65].

2.3.4 Cyclophosphamide

Cyclophosphamide is an alkylating agent. It crosslinks DNA and results in the death of activated lymphocytes and protects glomeruli [56, 66]. It modulates the expression of T and B cell activation markers [67]. It has been demonstrated in a meta-analysis that there is a decreased risk of end-stage renal disease when cyclophosphamide is applied as standard of care therapy for lupus nephritis [68]. Cyclophosphamide has potential side effects, which include leukopenia, infection risk, bladder toxicity and increased risk of malignancy [69]. Consequently, cyclophosphamide is used as an induction treatment for severe lupus [64, 70] and is replaced by other agents, such as MMF and azathioprine for long-term maintenance treatment.

2.3.5 Calcineurin inhibitors

The use of calcineurin inhibitors tacrolimus and cyclosporin A in SLE is derived from the experience of these drugs gained in organ transplantation. These drugs suppress the production of cytokines, inhibit T- and B cell activation and preserve the renal podocyte actin cytoskeleton, thus reducing proteinuria [71]. In non-renal SLE cyclosporin A exhibits steroid-sparing effects, reduces disease activity and flares [72]. Cyclosporin A acts by modulating lymphocyte function [73, 74]. It forms

a complex with cyclophilin to block the phosphatase activity of calcineurin. Thus, it decreases the production of inflammatory cytokines by T lymphocytes [75]. Tacrolimus is preferentially used for lupus nephritis as it exhibits fewer side effects and is characterized by better long-term outcome [76]. Tacrolimus is a macrolide antibiotic with immunosuppressive properties. It has a mode of action similar to that of cyclosporin A, although the two drugs are structurally unrelated. It exerts its effects principally through impairment of gene expression in target cells [77]. Tacrolimus bonds to an immunophilin and this complex inhibits calcineurin phosphatase. Tacrolimus inhibits calcium-dependent events, such as interleukin-2 gene transcription, nitric oxide synthase activation, cell degranulation, and apoptosis. It also potentiates the actions of glucocorticoids. It may enhance expression of the transforming growth factor beta-1 gene [78]. T cell proliferation, especially type 1 T helper cell, in response to ligation of the T cell receptor is inhibited by tacrolimus. Tacrolimus has been successfully applied in combination with low-dose MMF and corticosteroids as induction therapy in lupus nephritis [76, 79, 80]. Tacrolimus (0.075 mg/kg/day) has been used in refractory lupus nephritis with good results [81], however severe drug adverse events were observed, such as a high rate of infections and diabetic ketoacidosis. Cyclosporin A (2.6-3.7 mg/kg/day) has also been used in refractory lupus nephritis with good results, however drug adverse events such as tremor and hypertension have been noted [81]. Voclosporin, a novel calcineurin inhibitor is now used in lupus nephritis and is showing promising results [82].

2.3.6 Plasmapheresis

Plasmapheresis has been used successfully in refractory cases of neuropsychiatric lupus [83]. Plasmapheresis has also been applied in pregnant women with active lupus or antiphospholipid syndrome or in cases of lupus nephritis [84]. Immunoadsorption, is replacing plasmapheresis and appears to have good results [84].

2.3.7 Intravenous immunoglobulin

Therapeutic intravenous immunoglobulin (IV IG) mostly consists of human polyspecific immunoglobulin G. IV IG has been used in patients with systemic lupus erythematosus and was shown to reduce the activity of the disease [85]. IV IG may be used in cases of refractory neuropsychiatric lupus [83] and in lupus myocarditis [86].

2.4 Biologics

Biologic drugs currently incorporated in SLE treatment are rituximab [87–89] and belimumab [90–93] (**Figure 1**). The sequential use of rituximab and belimumab is also under investigation [94, 95]. Other biologic agents targeting the B lymphocyte have also been applied [96]. Various biologic drugs have been used in treatment regimens for SLE patients with poor response or side effects to standard treatment [97]. The original goal of biologics was to induce disease remission and establish self-tolerance [98, 99]. This goal has not been achieved. It may be that the heterogeneity of disease mechanisms inherent in SLE may guide the introduction of cell- and cytokine- or pathway specific therapies which will be effective in various subgroups of SLE patients [97].

2.4.1 Rituximab

Rituximab is a humanized anti-CD20 monoclonal antibody used for B cell depletion therapy. Rituximab can induce killing of CD20+ cells via various mechanisms.

The effects of rituximab include complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity [100]. Targeting the B cell has been proposed by many research studies in SLE [101]. Results from various registries have shown a favorable benefit-risk ratio in treatment refractory SLE [102, 103]. Rituximab has been shown to be safe and effective in the treatment of non-renal SLE [103]. Namely, it decreases disease activity, immunologic parameters and has a steroid-sparing effect. It can be recommended for organ-specific manifestations, such as arthritis and thrombocytopenia. Rituximab has been shown to be effective for certain refractory SLE patients, in particular refractory neuropsychiatric SLE [104]. Thus, it can be administered in this patient group. The therapeutic effect of rituximab has been compared with that of MMF and with that of cyclophosphamide in a trial of 54 lupus nephritis patients and was shown to be equally effective [105]. B cell depletion is observed but it is not complete, because early B cells and plasma cells do not express CD20 [106]. Normalization of B cell subsets has been observed in rituximab-treated SLE patients [101]. In the initial introduction of rituximab, it was suggested that complete B cell depletion might confer a better outcome for SLE [101]. However, SLE flares were observed after repeated rituximab infusions. These flares were thought to be a result of elevated circulating CD257 (BLyS) levels and high anti-dsDNA levels [107, 108]. Thus, it was proposed that B cell depletion with rituximab induced a surge in CD257 levels that may have exacerbated disease in some SLE patients [106]. In these individuals, rituximab depletion was followed by rapid peripheral B cell reconstitution, with increased circulating plasmablasts. It has been suggested that these plasmablasts might stimulate autoreactive T helper cells, which promote autoantibody production and may drive a positive feedback loop promoting disease activity [106]. Consequently, rituximab is considered in lupus nephritis only after cyclophosphamide and MMF have failed or in relapses [109]. Despite that, an analysis of the LUNAR study showed complete response with rituximab in cases of lupus nephritis [110].

2.4.2 Belimumab

Belimumab, the anti-CD257 monoclonal antibody, acts as a soluble CD257 antagonist and was the first drug approved in more than 50 years by the FDA for SLE [111–118]. The recognition of B cells as central in the pathogenesis of SLE led to the development of drugs that block B cells, including antibodies to B-cell surface antigens, B-cell tolerogens, blockers of co-stimulatory molecules and inhibitors of cytokines with direct effect on B cells [119]. The BAFF/APRIL axis has been thoroughly investigated as these cytokines are vital to B-cell maturation and survival [115, 120, 121]. Belimumab is an anti-BAFF antibody. Belimumab should be considered in extrarenal lupus in patients with inadequate response to hydrochloroquine and corticosteroids and immunosuppressive drugs [122]. Patients with cutaneous and musculoskeletal manifestations are expected to respond better. Belimumab was tested in a study in which it was administered in lupus patients after rituximab [123]. The effects of belimumab on proteinuria and neuropsychiatric SLE were examined in a recent study. It was found that belimumab decreased proteinuria and improved neuropsychiatric symptoms in neuropsychiatric SLE [124]. The US Food and Drug Administration (FDA) has expanded the indication for belimumab to adults with active lupus nephritis who are receiving standard therapy. The expanded indication for belimumab for patients with LN is based on findings from the BLISS-LN phase 3 trial. In this randomized placebo controlled clinical trial on the effect of belimumab on lupus nephritis it was shown that belimumab led more patients to a primary efficacy renal response than placebo and also led to a complete renal response more patients than the placebo [125]. The risk of a renal related event or death was lower among patients receiving belimumab.

2.4.3 Obinutuzumab

Obinutuzumab is a novel humanized type II glycoengineered anti-CD20 antibody [126]. In vitro studies have shown that obinutuzumab may induce superior B cell cytotoxicity as compared to rituximab in patients with SLE [126]. Obinutuzumab is considered an alternative B-cell depleting agent for the treatment of SLE [127]. It has been suggested that SLE patients with secondary non-response to rituximab should be preferentially switched to another B-cell depleting agent instead of belimumab [128].

2.4.4 Ofatumumab

Ofatumumab is a fully human anti-CD20 monoclonal antibody [129]. It induces antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity in CD20-expressing B lymphocytes. Ofatumumab is highly potent in lysing B cells, as this appears to stem from its binding site on the short extracellular loop of the target CD20 protein and its slow release from the target molecule. Ofatumumab has been successfully applied in a patient with SLE and hypocomplementemia in combination with fresh frozen plasma [130]. Ofatumumab, has been used as B cell depleting therapy in SLE patients who developed severe infusion reactions to rituximab [131]. The agent was well tolerated and may be a safe and effective alternative to rituximab for B cell depletion treatment in SLE.

2.4.5 Epratuzumab

Epratuzumab is a humanized monoclonal antibody [132]. It targets CD22 on B cells and acts as B-cell modulating treatment through inhibition of B-cell receptor signaling. It has been applied in SLE [133] and found to be effective in SLE patients with Sjogren's syndrome [134].

2.4.6 Sifalimumab

Interferons (IFNs) are a family of potent immunostimulatory cytokines that are broadly divided into three subtypes, type I, type II and type III [135]. Of all the type I IFNs, IFNα is the most abundant and is well characterized. The role of interferons in autoimmunity, especially SLE is discussed [136]. Sifalimumab is a fully human monoclonal antibody against multiple IFN-α subtypes and has shown promise in a phase IIb clinical trial in SLE [137].

2.4.7 Rigerimod

Rigerimod is a peptide which reduces the stability of MHC molecules that present antigens to T cells, thus blocking antigen presentation to autoreactive T cells thereby blocking B cell maturation. It has been tested in SLE patients with encouraging results [138].

2.5 Supplementary therapeutic modalities

Recently efforts have been made to incorporate adjunct therapeutic agents in the treatment of SLE, so, as to reduce the toxicity of traditional drugs. Prasterone and vitamin D are two immunomodulatory agents, which have been applied in the treatment of SLE as supplements, in order to control disease activity and reduce the use of corticosteroids. Prasterone is a synthetic form of the hormone dehydroepiandrosterone [139]. Its use led SLE patients to better tolerate the tapering of corticosteroids [140]

and stabilized disease activity in some patients [141]. Vitamin D has immunomodulatory properties, namely it decreases inflammatory cytokines and down regulates the renin-angiotensin system [142, 143]. It may lead to the improvement of disease activity in SLE, as shown by some but not all studies [144–146].

3. Therapeutic strategies for the management of SLE

In 2014 a panel of experts introduced the treating-to-target approach in the management of SLE [147]. In 2019 an update of the EULAR recommendations for the management of SLE was published [148]. These recommendations are based both on evidence as well as on expert opinion. According to these recommendations, hydroxychloroquine should be administered to all lupus patients at a dose not exceeding 5 mg/kg real body weight. During chronic maintenance therapy glucocorticoids should be minimized to less than 7.5 mg/day and withdrawn if possible. Initiation of immunomodulatory agents can aid in tapering or withdrawal of corticosteroids. In active or flaring extra-renal disease belimumab should be considered. Rituximab is an option for organ-threatening refractory disease. Various approaches for the treatment of SLE are currently under investigation. These include various methods to target interferon I, such as the use of anifrolumab, a human monoclonal antidoy to type I interferon receptor subunit 1 [149, 150], and to inhibit T cell co-stimulation [151]. Baricitinib, an oral selective Janus kinase1 and Janus kinase 2 inhibitor is an oral treatment, which was tested in SLE patients with favorable results [152].

4. Conclusion

Hydroxychloroquine and prednisone remain standard of care treatment for SLE. When flares occur the introduction of immunosuppressive agents and/or biologic drugs improves disease activity and disease outcome in SLE. Nowadays, the introduction of biologic agents, such as rituximab and belimumab have revolutionized the treatment of SLE and have opened new therapeutic horizons in all the spectrum of lupus disease.

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