Novel Biological Treatments for Systemic Lupus Erythematosus: Current and Future Modalities

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ABSTRACT: Current treatments for systemic lupus erythematosus (SLE) are effective in reducing morbidity and mortality but are not specific and have severe adverse effects. Based on understanding of the different dysregulated immunological pathways involved in SLE pathogenesis, specific targeted therapies were developed. This review presents the current and the near-future novel biological immune targeted treatments, such as B cell-targeted therapy, cytokine blockade, peptide-based treatments and other novel treatments for SLE.

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KEY WORDS: systemic lupus erythematosus (SLE), biological therapy, B lymphocytes, cytokine blockade, peptides

Systemic lupus erythematosus is a chronic multisystem disease of unknown etiology. It affects all races, although the disease is more common among African Americans, Hispanics and Asians. SLE is more prevalent in women, particularly during their childbearing years, with a male to female ratio of 1:9 [1]. The clinical manifestations of SLE are diverse, ranging from fatigue and oral ulcerations to life-threatening renal and neurologic disease. Disease activity fluctuates with periods of remissions and flares [1]. Although the precise etiology for SLE is not defined, genetic, hormonal, environmental and infectious factors appear to play a role in the pathogenesis of the disease. SLE is characterized by dysregulation of both the innate and the adaptive immune systems with the production of various autoantibodies and cytokines, as well as impaired T cell function and enhanced apoptosis [1].

The current treatment for SLE includes non-steroidal anti-inflammatory drugs, antimalarial agents, corticosteroids, high dose immunoglobulins, and cytotoxic immunosuppressive agents such as azathioprine, cyclophosphamide, methotrexate and mycophenolic acid. These treatments are quite effective, but they are not specific and have severe adverse effects. Based on knowledge of the different dysregulated immunological pathways involved in SLE pathogenesis, specific targeted therapies

were developed. This review presents the current and the near-future novel immune targeted treatment modalities for SLE.

B CELL-TARGETED THERAPY

The hallmark of SLE is B cell activation and the production of various autoantibodies. Therefore, biologics that target B cells may be an effective therapy for SLE via the reduction of autoantibody production and by prevention of antigens presenting to T cells.

RITUXIMAB (ANTI-CD20 MAB)

Rituximab is a chimeric monoclonal antibody specific for human CD20, a B cell surface antigen expressed only on mature B cells. Thus, RTX causes selective transient depletion of the CD20+ mature B cells.

Several open uncontrolled studies reported the efficacy of RTX in the treatment of lupus patients who had failed to respond to standard treatment. Leandro et al. [2] reported clinical and serological (C3, anti-dsDNA) improvement following RTX treatment in their open study of 24 lupus patients who had failed immunosuppressive therapy. In another retrospective uncontrolled study of 31 lupus patients (17 with nephritis, 14 with cytopenia) who did not respond to conventional immunosuppressive treatment, Lindholm and co-workers [3] demonstrated beneficial effects following the addition of RTX to the treatment regimen. Looney et al. [4] reported a series of 17 patients with refractory lupus nephritis who were treated (in an open uncontrolled study) with increasing doses of RTX. Clinical improvement was observed in 11 patients who achieved profound B cell depletion. In the later study the clinical efficacy was not accompanied by a reduction in anti-dsDNA autoantibody levels [4]. Several other uncontrolled studies also suggested beneficial effects of the addition of RTX to the standard treatment regimens (steroids and cytotoxic agents) for refractory lupus patients (including patients with nephritis and neuropsychiatric lupus) [5]. The clinical improvement in the above uncontrolled studies was observed in 60–80% of the patients and was always accompanied by transient B cell depletion. Severe infections were reported in 5–10% of the RTX-treated

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SLE = systemic lupus erythematosus

RTX = rituximab

patients [6]. It should be noted that these promising results were not confirmed by two randomized multicenter controlled trials [7,8]. In 257 lupus patients without nephritis (EXPLORER), RTX was administered intravenously (two rounds of 1000 mg) but failed to demonstrate efficacy over placebo [7]. However, a post hoc analysis of the EXPLORER study suggested that RTX reduced the risk of severe lupus flares as defined by BILAG [7]. Similarly, RTX was not proven superior to placebo in lupus patients with nephritis (LUNAR trial) [8]. The relatively short follow-up period (52 weeks) as well as the concomitant use of steroids and immunosuppressive agents in those two controlled studies may explain the lack of RTX benefit. Recently, Terrier and associates [6] presented the prospective data of the French AutoImmunity RTX Registry. In that French cohort, 136 lupus patients were treated with RTX (in addition to standard treatment). Severe infections were noted in 12 patients (9%) mostly within 3 months after RTX infusion. Articular, cutaneous, renal and hematological improvements were observed in 72%, 70%, 74% and 88% of the RTX-treated patients, respectively.

Taken together, the role of RTX in the treatment of SLE is still controversial. Its clinical benefit was not proven in two large controlled clinical trials [7,8]; however, several open-label or retrospective studies including the large French Registry (136 patients) [6] suggested that adding RTX to the standard treatment regimen is beneficial. Thus, RTX is currently not an approved agent for the treatment of SLE. Nevertheless, in refractory SLE patients (especially in patients with immune mediated cytopenia and nephritis) the addition of RTX to the immunosuppressive treatment (as an off-label drug) may be considered.

Intensive research of the pathogenesis of systemic lupus erythematosus resulted in novel specific treatment modalities

The most frequent adverse effects of RTX treatment are mild infusion reactions [6]. Neutropenia and severe infections were reported in up to 10% of the treated patients [6]. Two cases of multifocal leukoencephalopathy were reported in SLE patients who received RTX. Thus, RTX should be avoided or used with caution in lupus patients with central nervous system involvement.

BLyS-TARGETED THERAPY

B lymphocyte stimulator, also known as BAFF (a member of the tumor necrosis ligand superfamily), is a key factor in maturation and survival of B cells. BLyS protein is expressed as a cell surface protein by a wide variety of cells. On the cell surface BLyS molecules are organized as a trimmer. Following a cleavage by furin protease BLyS is released into the circulation as a biologically active soluble protein [9]. The soluble form of BLyS can bind three receptors: TACI (transmembrane activator and calcium modulator, and cyclophilin ligand interactor), BCMA (B cell maturation antigen), and BLyS receptor 3 (BR3) also known as

BAFF-R. The agonist effects of BLyS on B cells are mediated predominantly through the BAFF-R/BR3 receptor. BLyS is the sole ligand of BR3/BAFF-R, whereas TACI and BCMA can also bind other TNF family ligands [9]. BLyS over-expression is a feature of SLE. In a cross-sectional study, 40% of the patients with SLE appeared to have significantly high levels of circulating BLyS protein compared to controls. Plasma BLyS levels appear to correlate with immunoglobulin G levels and anti-dsDNA autoantibody titers. Higher BLyS levels were associated with disease activity, as defined by the SELENA-SLEDAI score [10]. Thus, BLyS antagonism may be beneficial in the treatment of SLE.

BELIMUMAB

Belimumab is a human monoclonal antibody (IgG1) that binds soluble BLyS, thus inhibiting its binding to TACI, BCMA and BR3 receptors [9]. The efficacy and safety of belimumab in SLE patients has been studied in a number of trials. Furie et al. [11] randomized 70 SLE patients with mild to moderate disease to receive treatment with four different doses of belimumab or placebo (phase I study). During the 84–105 day follow-up period, belimumab was well tolerated without significant adverse events as compared to placebo. In a phase II belimumab trial, Wallace et al. [12] randomized 449 SLE patients to receive belimumab or placebo in three doses (a 52 week study). Similar to the phase I study, belimumab was well tolerated without significant adverse events compared to placebo. Furthermore, belimumab treatment led to a significant reduction of naïve activated CD20+ B cells. However, the trial failed to meet its primary endpoint (reduction in the SELENA-SLEDAI score) despite the 30% reduction in anti-dsDNA autoantibody titers. Recently, two large phase III trials (BLISS-52, BLISS-76) of 1684 SLE patients with mild to moderate disease activity (without active nephritis or active central nervous system disease) were reported [reviewed in 13]. In these trials, patients were treated with placebo, 1 mg/kg or 10 mg/kg of belimumab in addition to standard therapy. Both studies demonstrated the superiority of belimumab at the dose of 10 mg/kg over placebo at 52 weeks. The primary endpoint in these trials was a new index called SRI (SLE responder index), which combines the SELENA-SLEDAI and the BILAG scores. Response was observed in 44%, 58% and 51% for the placebo, 10 mg/kg and 1 mg/kg of belimumab, respectively. Moreover, belimumab reduced SLE-related flares and had a steroid-sparing effect [13]. It should be noted that severe lupus

BLyS = B lymphocyte stimulator

BR3 = BLyS receptor 3
TACI = transmembrane activator I
BCMA = B cell maturation antigen
TNF = tumor necrosis factor
IgG1 = immunoglobulin G 1

patients (active CNS, nephritis) were not included in these trials and most of the patients had arthritis and mucocutaneous involvement [13]. Furthermore, although the beneficial effects of belimumab compared to placebo were statistically significant, they were quite modest. Nevertheless, this drug, currently called Benelysta® (Glaxosmithkline, Canada), was approved (March 2011) by the U.S. Food and Drug Administration for the treatment of mild to moderate SLE.

APRIL-TARGETED THERAPY

Another member of the TNF-ligand super family is APRIL, a proliferation-inducing ligand. BLyS and APRIL share signaling via TACI and BCMA receptors. As mentioned above, BLyS binds specifically to the BR3 whereas APRIL can bind with low affinity to heparin sulfate proteoglycans in addition to its binding to the TACI and BCMA receptors [9]. Atacicept (formerly known as TACI-Ig) is a recombinant fusion protein containing the extracellular, ligand-binding portion of the TACI receptor with the Fc portion of human IgG. Atacicept binds to BLyS and APRIL, inhibiting their binding to B cells. In mice, atacicept has been shown to reduce mature B cell counts and serum antibody levels. In a phase Ib study, Dall'Era et al. [14] assessed the safety and tolerability of atacicept in 49 patients with mild to moderate SLE. Treatment with atacicept was associated with an initial transient increase in mature and total B cells followed by a sustained dose-related reduction of B cells as well as dose-dependent reductions in immunoglobulin levels. Atacicept was well tolerated without significant adverse events [14]. Although this small study suggested that atacicept may be beneficial in lupus patients, other larger studies are needed to define the role of atacicept in the treatment of SLE. Currently atacicept is not considered a treatment option for lupus patients.

Belimumab (anti-BLyS) was approved by the FDA for treatment of SLE patients with mild to moderate disease

EPRATUZUMAB (ANTI-CD22 MAB)

CD22 is a 135 kDa glycoprotein expressed exclusively on mature B cells but not on plasma cells. CD22 was reported to play a role in regulating B cell apoptosis. In a 32 week open-label study, 14 lupus patients with moderate disease (BILAG 6-12) were treated with four doses of 360 mg/m² epratazumab (a humanized anti-CD22 IgG1 mAb). The drug was well tolerated without serious adverse events. The treatment caused transient (6 months) B cell depletion and led to clinical improvement (50% reduction in BILAG score in all 14 patients) [15]. Two 48 week placebo-controlled phase III trials (SL0003, SL0004) recruited 90 patients with severe disease (BILAG A or B scores in at least two systems). The patients were treated with two

CNS = central nervous system
mAb = monoclonal antibody

doses of epratuzumab (360 mg/m² or 720 mg/m²) or placebo twice every 12 weeks. Epratuzumab was well tolerated (in both doses). Significant B cell reduction was observed compared to placebo (35% for the lower dose and 72% for the higher dose of epratuzumab). Furthermore, epratuzumab treatment, at both doses, resulted in a better reduction of total BILAG scores (6.9, 9.0 and 5.4 at week 48 for epratuzumab 360 mg/m², 720 mg/m² and placebo, respectively). In addition, epratuzumab treatment enabled significant steroid sparing and improved quality of life compared with placebo [16]. Based on those promising results, a phase III open continuation study (of 30 SL0003/SL0004 patients) and a new large randomized placebo-controlled phase III study are currently in progress.

ABETIMUS SODIUM (FORMERLY LJP 394)

Abetimus sodium is a molecule composed of four identical dsDNA epitopes conjugated to a small molecule platform. Abetimus sodium is capable of cross-linking anti-dsDNA antibodies in solution and on the surface of B cells. Clinical studies have shown that intravenous administration of abetimus sodium resulted in rapid and sustained reduction of circulating anti-dsDNA autoantibody levels [17]. Given the importance of anti-dsDNA antibodies in the pathogenesis of lupus nephritis, studies were designed to evaluate whether treatment with abetimus sodium could prolong the time to renal flare in patients with lupus nephritis. In a randomized controlled phase II trial, abetimus sodium failed to prolong the time to renal flare as compared with placebo [17]. A retrospective analysis of the later study defined a subgroup of patients with high affinity antibodies to abetimus DNA epitopes who had significantly better clinical outcome, including longer time to renal flare, following abetimous sodium treatment [17]. In a phase III trial called ASPEN (abetimus sodium in patients with history of lupus nephritis), abetimus sodium significantly reduced anti-dsDNA autoantibody levels but failed to prolong time to renal flare [18]. To the best of our knowledge, there are no current clinical trials with abetimus sodium and this agent is not used for the treatment of lupus.

INHIBITION OF T CELL ACTIVATION

ABATACEPT – CTLA-4IG (CD152)

The interaction between CD40 (on B cells) and its ligand CD40L (CD154) on T cells is crucial for the T cell-dependent B cell activation and differentiation. Inhibition of CD40-CD40L pathway by anti-CD40L antibodies was effective in murine SLE but was not safe or effective in lupus patients [19]. Another co-stimulatory immune interaction includes CD28 and CTLA4 (CD152) on T cells and their ligands CD80 and CD86 on anti-

gen-presenting cells and B cells. Abatacept is a soluble fusion protein of CTLA4 linked to the Fc portion of human IgG1. The blockade of CD80/86 interaction with CD28/CTLA4 on T cells inhibits T cell activation. Indeed, CTLA4Ig was shown to be effective in the treatment of lupus of (NZBXNZW)F1 mice (prolonged survival, reduced renal disease) [20]. However, in a phase IIb randomized double-blind placebo-controlled trial of 175 lupus patients without nephritis CTLA4Ig did not reduce disease activity (defined by SLEDAI) over placebo [21]. Currently abtacept is not used for the treatment of SLE.

CYTOKINE BLOCKADE-TARGETED TREATMENT

An alternative way to directly target immune cells is to interfere with their messengers, the cytokines. Dysregulation in the production of various cytokines was reported in SLE [1]. Thus, normalization of those cytokine abnormalities may improve disease activity.

TNFα INHIBITION IN SLE

Tumor necrosis factor-alpha is an important pro-inflammatory cytokine involved in the activation of inflammatory events leading to tissue destruction [22]. TNFα was shown to be increased in the sera of SLE patients with active disease. Moreover, TNFα was found in renal tissue of lupus patients with glomerulonephritis and its level was associated with renal disease activity [22]. Thus, anti-TNFα therapy may be beneficial in the treatment of lupus.

Several biological treatments for SLE are currently being investigated in clinical trials

INFLIXIMAB (REMICADE®, SCHERING PLOUGH, USA)

Infliximab is chimeric mAb anti-TNFα. In an open study, six patients with moderately active SLE (four with nephritis and three with arthritis) refractory to standard therapies were treated with infliximab in addition to Imuran® (Perrigo, USA) or methotrexate. Infliximab treatment resulted in the amelioration of both proteinuria and arthritis. However, the titers of anti-dsDNA and anticardiolipin IgG autoantibodies significantly increased in the infliximab-treated patients [22]. In another pilot study, of nine SLE patients treated with infliximab four dropped out due to infliximab infusion reactions; the other five patients showed improvement in disease activity (SLEDAI) [23].

ETANERCEPT (ENBREL®, AMGEN, USA)

Etanercept is a recombinant TNFα receptor that binds to soluble TNFα, reducing its biological activity. No clinical trials or studies have investigated the role of Enbrel in SLE patients. Since anti-TNFα agents were reported to induce the generation of autoantibodies [22] and rarely to induce clinical SLE [24], it is unlikely that TNFα blocking will be used for the treatment of SLE.

HUMAN RECOMBINANT IL-I RECEPTOR ANTAGONIST (ANAKINRA, KINERET® AMGEN, USA)

The interleukin-1 family comprises three structurally related polypeptides, IL-1α, IL-1β and the endogenous IL-1 receptor antagonist IL-1Ra. IL-1α and IL-1β are primarily synthesized by activated monocytes and macrophages. IL-1 induces activation of T cells and promotes chemotaxis of polymorphonuclear cells, leukocytes, lymphocytes and monocytes, stimulates protease release by tissue macrophages, and enhances infiltration of these molecules into inflamed tissue. IL-1Ra, discovered in 1980, is an endogenous specific receptor antagonist that inhibits the pro-inflammatory effects of IL-1 by binding IL-1, thereby preventing its binding to the cellular receptor.

High levels of IL-1β were reported in the sera and cerebrospinal fluid of lupus patients. Although high IL-1Ra levels were also found in the sera of lupus patients, its levels are not sufficient to block IL-1 activity especially in patients with lupus nephritis [25]. Anakinra, a recombinant human IL-1 receptor antagonist, was shown to block IL-1 and to be beneficial in the treatment of severe rheumatoid arthritis. Two very small uncontrolled studies of three and four SLE patients suggested that anakinra might have beneficial effects on musculoskeletal lupus-related manifestations [26]. To the best of our knowledge, there are no current clinical trials with anakinra or with the other IL-1Ra, cankinumab.

ANTI-IL-6 RECEPTOR ANTIBODY (ACTEMRA, TOCILIZUMAB®, ROCHE, SWITZERLAND)

IL-6 is a multifactorial cytokine produced by macrophages, monocytes, T and B cells. IL-6 exerts a broad range of biological activities on various target cells. It stimulates B cell differentiation, immunoglobulin secretion and T cell function. Elevated levels of IL-6 were found in the sera of lupus patients with a correlation to disease activity [27]. In a murine model of SLE, administration of anti-IL-6 mAb suppressed the production of anti-dsDNA autoantibodies and the SLE-related kidney disease. Tocilizumab is a humanized mAb against the alpha-chain of IL-6 receptor. Recently the effects of increasing doses of tocilizumab (2, 4, 8 mg/kg intravenously every other week for 12 weeks) in 16 lupus patients with mild to moderate disease activity were studied in an open phase I trial [28]. Tocilizumab was well tolerated (although significant neutropenia was observed). In addition, tocilizumab treatment resulted in significant clinical improvement (≥ 4 SLENA-SLEDAI index points), especially in patients with arthritis [28]. Based on these encouraging results, a new placebo-controlled phase II/III study is currently underway.

TNFα = tumor necrosis factor

IL = interleukin

ANTI-IL-10 ANTIBODY

IL-10 is produced by activated macrophages and suppressor CD4+ T cells. SLE patients produce abnormally large amounts of IL-10 that correlate with disease activity [1]. In an SLE mouse model, anti-IL-10 mAb treatment led to a significant reduction in autoantibody production. Administration of murine anti-IL-10 mAb (21 consecutive days) to six patients with moderate lupus (an open study) resulted in improved healing of arthritis and cutaneous lesions. The treatment was well tolerated by the patients [29]. To the best of our knowledge there are no current clinical trials of anti-IL-10 in lupus patients.

INTERFERON-ALPHA INHIBITION (ANTI-IFNα)

Several lines of evidence suggest a major role for type I IFN (IFNα and IFNβ) in the pathogenesis of SLE. Increased levels of IFNα in the sera of patients with active lupus were reported; IFNα treatment of hepatitis C virus patients induced (in some patients) the production of autoantibodies and rarely clinical lupus; IFNα signature was found in blood cells of lupus patients (microarray studies); and animal studies demonstrated that type I IFN receptor deficiency (knockout) reduced lupus-related manifestations in (NZBxNZW)F1 mice [reviewed in 30]. Based on those observations, the efficacy of two anti-IFNα monoclonal antibodies (rontalizumab, sifalimumab) in the treatment of SLE is currently under study.

Zagury and colleagues [30] were able to demonstrate that injecting (NZBXNZW)F1 lupus-prone mice with adjuvant IFNα (IFNα kinoid) induced transient neutralizing anti-IFNα antibodies concomitantly with significant improvement of lupus-related manifestations, including proteinuria, kidney damage and survival. More recently, Mathian and collaborators [31] immunized mice with human IFNα (conjugated to KLH, INF-K). The mice produced antihuman IFNα antibodies that neutralized all 13 subtypes of human IFNα as well as IFNα obtained from the sera of active lupus patients. Currently, IFN-K immunization is being tested in phase I/II clinical studies in lupus patients.

PEPTIDE-BASED TREATMENTS

Several laboratories have succeeded in generating different small artificial peptides (based on autoantigens or autoantibodies) that have the ability to induce immunologic tolerance. These tolerogenic peptides were shown to change the course of SLE in mice models. Hahn et al. [32] reported the amelioration of SLE-like disease in mice by a 15 amino acid peptide based on sequences from heavy chains of four different (NZB x NZW)F1 anti-dsDNA autoantibodies (pConsensus).

Another tolerogenic peptide is a splisosomal peptide, an epitope present on residues 131-151 of the 70K spliceosomal protein within the U1small nuclear RNP (P140). In a phase II open-label trial of 20 moderately active SLE patients the peptide

IFN = interferon

was found to be safe and well tolerated. Treatment with the P140 peptide improved the clinical and serological status of lupus in eight of the patients [33]. A larger controlled clinical trial with P140, now designated Lupuzor® (ImmuPharm, England) is planned.

The hCDR1 peptide (edratide) is an immunomodulatory peptide derived from the 16/6 Id anti-dsDNA mAb. This peptide was proven beneficial in several murine lupus models [34]. The PRELUDE trial, which studied the tolerability, safety and effectiveness of edratide in the treatment of mild to moderate lupus, comprised 340 SLE patients. The peptide was found to be safe and well tolerated; however, the trial failed to reach its primary outcome – namely, reduction of SLEDAI as compared to placebo. However, a post hoc analysis demonstrated a significant reduction in the BILAG score (following edratide compared to placebo) especially in patients with high anti-dsDNA autoantibody titers [35]. Further clinical trials with the hCDR1 peptide in the treatment of SLE are currently planned.

OTHER NOVEL TREATMENTS

MEMANTINE

Subsets of anti-dsDNA autoantibodies (mainly nephrotoxic anti-dsDNA antibodies) cross-react with anti-NR2 (N methyl D aspartate-NMDA) receptor autoantibodies. Anti-NR2 autoantibodies in the sera of SLE patients were reported to correlate with cognitive impairment and learning deficits, but other studies failed to demonstrate such an association [36]. Memantine is an NMDA receptor antagonist approved by the FDA for the treatment of Alzheimer's disease. As a receptor antagonist (mimicking the NR2 receptor) memantine can bind the pathogenic cross-reactive (anti-dsDNA/NR2) autoantibodies, preventing their deposition in glomeruli and neuron cells, respectively. Nevertheless, in a randomized trial of lupus patients with mild cognitive impairment, memantine did not demonstrate significant beneficial effects [37]. To the best of our knowledge there are no current clinical trials of this agent in lupus patients.

STATINS

In addition to their effect on lipid metabolism, statins were shown to have immunomodulatory effects. Several studies aimed at determining the role of statins in murine lupus did not show consistent results. Similarly, small studies in SLE patients did not show significant beneficial effects for statins [38]. Thus, lowering lipid levels (when indicated) is the sole indication for statin treatment in lupus patients.

ANTIOXIDANTS

Reactive oxygen intermediates are generated during immune activation processes. Those ROI can damage endothelium, oxi-

FDA = Food and Drug Administration
ROI = reactive oxygen intermediates

dize cell membrane lipids, and induce apoptosis in various cell types. In addition, ROI can activate immune cells in a positive feedback mechanism [39]. Antioxidants like N-acetyl cysteine and cysteamine can reduce the ROI-induced tissue damage and immune activation. Both NAC and CYST were shown to be beneficial in the treatment of (NZWxNZW)F1 lupus-prone mice [39]. However, since studies of NAC or CYST in the treatment of SLE patients are lacking, these agents are not approved for the treatment of lupus. Nevertheless, those agents are safe and without adverse effects and one may consider adding NAC or CYST to standard treatment as an off-label drug.

VITAMIN D

Vitamin D is not only essential for mineral metabolism and skeletal health, it also has an effect on the cardiovascular and immune systems [40]. Lupus patients avoid the sun because of photosensitivity and potential disease flare. Thus, vitamin D deficiency is expected in those patients. Indeed, low levels of 25-OH Vit-D were demonstrated in the sera of lupus patients, with an inverse correlation to disease activity [40]. Although controlled clinical trials of vitamin D treatment in SLE are lacking, we highly recommend that levels be tested in all SLE patients and that all patients with vitamin D deficiency be treated.

CONCLUSIONS

Intensive research in recent years has increased our understanding of the pathogenesis of SLE. As a consequence, new therapeutic approaches and possibilities are being explored to find better treatment possibilities which will be more effective, more specific and less toxic [Table 1]. As mentioned above, the FDA recently approved Benlysta® (belimumab) for the treatment of mild to moderate SLE. This drug is the first new lupus drug approved in the last 56 years. We hope that more specific treatments will soon augment the range of therapeutic options for SLE.

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Table 1. Key biological treatments for SLE

Biological agent	Target	Current status	References
Rituximab (MabThera®)	CD20 (B cells)	Clinical trials failed, off-label usage	[2-8]
Belimumab (Benelysta®)	BLyS (B cells)	FDA-approved	[11-13]
Epratuzumab (LymphoCIDE®)	CD22 (B cells)	Clinical trial in progress	[15,16]
Tocilizumab (Actemra®)	IL-6 receptor	Clinical trial in progress	[27,28]
Anti-IFNα Sifalimumab (Rontalizumab®)	INFα	Clinical trial in progress	[30,31]
Rigerimod Lupozor® RNP-based peptide	Tolerogenic peptide	Clinical trial in the near future	[33]
hCDR1 edratide, hCDR1-based peptide	Tolerogenic peptide	Clinical trial in the near future	[35]

NAC = N-acetyl cysteine
CYST = cysteamine

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