Review

Novel approaches to the development of targeted therapeutic agents for systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic multisystem disease in which various cell types and immunological pathways are dysregulated. Current therapies for SLE are based mainly on the use of non-specific immunosuppressive drugs that cause serious side effects. There is, therefore, an unmet need for novel therapeutic means with improved efficacy and lower toxicity. Based on recent better understanding of the pathogenesis of SLE, targeted biological therapies are under different stages of development. The latter include B-cell targeted treatments, agents directed against the B lymphocyte stimulator (BLyS), inhibitors of T cell activation as well as cytokine blocking means. Out of the latter, Belimumab was the first drug approved by the FDA for the treatment of SLE patients. In addition to the non-antigen specific agents that may affect the normal immune system as well, SLE-specific therapeutic means are under development. These are synthetic peptides (e.g. pConsensus, nucleosomal peptides, P140 and hCDR1) that are sequences of conserved regions of molecules involved in the pathogenesis of lupus. The peptides are tolerogenic T-cell epitopes that immunomodulate only cell types and pathways that play a role in the pathogenesis of SLE without interfering with normal immune functions. Two of the peptides (P140 and hCDR1) were tested in clinical trials and were reported to be safe and well tolerated. Thus, synthetic peptides are attractive potential means for the specific treatment of lupus patients. In this review we discuss the various biological treatments that have been developed for lupus with a special focus on the tolerogenic peptides.

1. Introduction

Systemic lupus erythematosus (SLE, lupus) is a chronic multisystem disease of unknown etiology [1,2]. It affects all races though it is more common among African-Americans, Hispanics and Asians [1]. SLE is much more prevalent in females as compared to males (9:1 ratio) [2]. The prevalence of SLE is about 1:1000 females but it is increasing constantly due to both, a better early diagnosis and a better survival of lupus patients [1,2]. Disregulation of both, the innate and the adaptive immune systems play a role in the pathogenesis of lupus. The peptides are tolerogenic T-cell epitopes that immunomodulate only cell types and pathways that play a role in the pathogenesis of SLE without interfering with normal immune functions. Two of the peptides (P140 and hCDR1) were tested in clinical trials and were reported to be safe and well tolerated. Thus, synthetic peptides are attractive potential means for the specific treatment of lupus patients. In this review we discuss the various biological treatments that have been developed for lupus with a special focus on the tolerogenic peptides.

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severe lupus manifestations (e.g. renal or CNS involvement) but these agents also have significant short and long term adverse effects [7]. Moreover, although the above treatment modalities are quite effective they are not specific for lupus and the control of disease activity with those agents remains suboptimal. Thus, in spite of treatment, lupus patients have active lupus related flares in substantial fractions of their life [7]. Therefore, there is an unmet need for alternative nontoxic effective and more lupus specific therapeutic approaches.

Based on the knowledge of the different dysregulated innate and adaptive immunological pathways involved in the pathogenesis of SLE, attempts have been made to develop biological therapies against targets that play a role in lupus. The various therapeutic means are at different stages of development. In general, they could be divided into non-specific and SLE specific means. The non-specific approaches could be further categorized as cell depleting agents and immunomodulatory means. In the present article we review the various biological therapeutic agents with a special focus on lupus antigen-specific therapeutic means.

2. B-cell targeted treatments

B cell activation with excess generation of immunoglobulins and autoantibodies is the hallmark of SLE [1,2,8]. Therefore, biological agents that target B cells and reduce their activity have been developed as potential candidates for the treatment of lupus [8].

2.1. Rituximab (anti-CD20 mAb)

Rituximab (Fig. 1; 1) is a chimeric monoclonal antibody (mAb) against CD20, a B cell surface antigen expressed on mature B cells but not on plasma cells [8]. Upon binding to its target, Rituximab enhances B cell apoptosis and depletion [9]. Rituximab was shown to be effective in the treatment of B cell malignancies [10] as well as Rheumatoid Arthritis [11]. Several open uncontrolled studies suggested the efficacy of Rituximab in the treatment of lupus patients (with or without renal involvement) who failed to respond to standard treatment modalities [9,12–14]. Recently, Terrier et al., reported significant therapeutic effects of Rituximab in 136 lupus patients with musculoskeletal, cutaneous, hematological and renal involvement (The French Rituximab registry) [15]. However, two large controlled clinical trials, the LUNAR in patients with lupus nephritis [16] and the EXPLORER in patients with other (non-renal) SLE manifestations [17] failed to demonstrate significant beneficial therapeutic effects for Rituximab. Factors like study design and size, background treatment and the chosen primary end points may explain the discrepancy between the uncontrolled studies and the above controlled clinical trials [5,9,18]. Although the role of Rituximab treatment in SLE is still controversial because the controlled trials do not support its routine use [16,17], both the American College of Rheumatology and the European League against Rheumatism (EULAR) have included Rituximab as an appropriate off-labeled treatment for refractory lupus patients with hematological or renal disease, after conventional therapy had failed [19,20]. The main adverse events of Rituximab are infections reported in up to 10% of the treated patients [15]. Progressive multifocal leukoencephalopathy (PML) was reported in two lupus patients following treatment with Rituximab though the causative role of Rituximab for the PML was not proven [15].

2.2. Epratuzumab (Anti-CD22 mAb)

CD22 is a 140kD surface protein, expressed on most mature B cells. It has a role in controlling B cell responses (via the B-cell receptor; BCR) to antigens [21]. Epratuzumab (Fig. 1; 2), a humanized IgG1 anti-CD22 mAb, was shown to reduce (in vitro) the expression of CD22, CD15, CD21 and CD79b on the surface of peripheral B cells obtained from healthy donors and lupus patients. The reduction of those molecules appears to result from both, internalization of CD22 (via the F(ab)2 fragment) and a specific phagocytosis mechanism — transfer of B cell surface molecules to monocytes and NK cells via the Fc fragment [21]. Thus, in addition to the induction of B...
cell depletion (which is less prominent compared to Rituximab), Epratuzumab has unique immunoregulatory effects [21,22]. Two studies reported clinical improvement, compared to placebo, in 14 (phase I) and 90 patients (ALLEVIATE-1/2 trials) [21] with active lupus disease following Epratuzumab treatment. Epratuzumab was well tolerated without severe adverse events [21]. A 12-week phase IIb (EMBLEM) randomized, double-blind, placebo-controlled multicenter study was further conducted with Epratuzumab. The study included 227 patients with a moderate to severe lupus disease activity without active renal or central nervous system involvement (mean BILAG and SLEDAI scores of 15.2 and 14.8, respectively). Treatment with Epratuzumab 2400 mg cumulative dose was well tolerated and associated with improvements in disease activity [23]. Two multinational, phase III trials (EMBODY), are in progress and should clarify the actual role of Epratuzumab in the treatment of lupus patients.

3. BLyS targeted therapy

B lymphocyte stimulator (BLyS), also known as B cell activating factor (BAFF), is a 285 amino acid transmembrane protein (expressed on the surface of monocytes, macrophages, dendritic and activated T cells) that belongs to the tumor necrosis factor ligand superfamily [24–26]. Following a cleavage by purin protease, soluble active BLyS (17Kd protein) is released into the circulation [26]. The soluble BLyS can bind to three receptors (BCMR – B cell maturation antigen, TACI – transmembrane activator and calcium modulator and cyclophilin interactor and BR3 – BLyS/BAFF receptor 3) on the surface of B cells [24]. BLyS is a growth factor for B-cell maturation, activation, and survival [27,28]. It was suggested that autoreactive B cells have a higher dependency on BLyS for their survival compared to non-autoreactive ("normal") B cells [29]. BLyS was shown to play a role in the pathogenesis and course of murine lupus [30,31]. In addition, high BLyS levels were shown in sera of lupus patients [32,33]. Another member of the B lymphocyte stimulator family, the proliferation-inducing ligand (APRIL) was shown to bind to the BCMA and TACI but not to the BR3 BLyS receptors on B cells [34].

3.1. Belimumab (anti-BLyS mAb)

Belimumab (Fig. 1; 3) is a fully humanized IgG1 mAb that binds to soluble BLyS, preventing its binding to the B-cell receptors (BR3, BCMA and TACI) thus inhibiting BLyS activity [32]. The efficacy and safety of Belimumab in the treatment of lupus patients was studied in several trials [35,36]. Two large phase 3 placebo controlled clinical trials (BLISS-52 [37] and BLISS-76 [38]) of 1684 lupus patients with mild to moderate disease activity (without lupus nephritis/CNS) demonstrated significant clinical response with 10 mg/kg of Belimumab as compared to placebo. The beneficial effects in the BLISS trials were measured by the SLE responder index (SRI) that combined the SLE disease activity index (SLEDAI), the British island lupus assessment group (BILAG) and the physician’s global assessment (PGA) at week 52 [37–39]. The SRI in the combined BLISS trials was 39%, 46% and 51% for the placebo, 1 mg/kg and 10 mg/kg treated groups, respectively [39]. Belimumab treatment (at 10 mg/kg) also reduced SLE-related flares, normalized C3 and C4 levels and had a steroid sparing effect [37–39]. The beneficial effects of Belimumab over placebo appeared 16–24 weeks following the initiation of the treatment and persisted through 52 weeks [37–39]. Based on the results of the BLISS trials, Belimumab was approved by the FDA for the treatment of SLE patients on March 2011 and became the first drug approved for SLE for over 50 years [40]. It should be noted that a large percentage of the patients did not respond to Belimumab treatment [37–39]. In addition, Belimumab was less effective among African-American patients [39]. Moreover, although statistically significant, the beneficial effect of Belimumab was modest and shown only in patients with mild to moderate (mainly mucocutaneous and musculoskeletal) disease [39]. The rate of infections originated from B cell depletion, was not significantly higher with Belimumab as compared with placebo. Infusion reactions were reported in 13.6% of the Belimumab treated patients (9.8% in the placebo) [37,38,41]. Depression with or without suicidal thoughts was reported following Belimumab treatment [39].

3.2. Atacicept

Atacicept (Fig. 1; 4) is a fully humanized fusion protein combining the Fc portion of IgG and the TACI receptor that binds BLyS as well as APRIL thus inhibiting both B-cell stimulating factors [42]. In a phase Ib study (49 patients with mild to moderate lupus), Atacicept was reported to be safe, well tolerated and had beneficial therapeutic effects [43]. However, the phase I/II randomized controlled trial of Atacicept in patients with lupus nephritis (background treatment included corticosteroids and Mycofenolate Mofetil) was prematurely terminated due to safety concerns (increased proteinuria, severe pneumonia) [44]. Thus, despite its theoretical potential, currently Atacicept has no role in the treatment of SLE.

3.3. Blisibimab

Blisibimab (Fig. 1; 5) is a fusion between the Fc portion of IgG and a peptide that binds to both, soluble and membrane bound BLyS. A phase II clinical trial studying its role in the treatment of SLE is currently in progress [24].

3.4. Tabalumab

Tabalumab (Fig. 1; 5) is a mAb directed against both, soluble and membrane bound BLyS. In contrast to the intravenous administration of Belimumab, Tabalumab is given subcutaneously. Two phase III clinical trials (NCT01205438, NCT01196091) aimed at assessing the efficacy and safety of Tabalumab in SLE patients are currently in progress [24].

4. Inhibition of T-cell activation

The activation of T cells requires at least two independent signals. The first signal results from the engagement of the MHC complex and the antigen with the T cell receptor. The second activation signal is an antigen-independent event which involves an interaction of co-stimulatory molecules such as CD28 (expressed on T cells) and CD80/CD86 (expressed on antigen presenting cells such as DC, macrophages or B cells). Another co-stimulatory pathway is the interaction between CD40 (on B cells) and the CD40 ligand (CD40L, on T cells) [45]. Inhibition of T cell co-stimulation is expected to be effective in lupus treatment [46]. Nevertheless, monoclonal antibodies against CD40 or CD40L were reported to be ineffective in lupus treatment and were associated with thromboembolic adverse events [47,48].

4.1. Abatacept (CTLA-4lg)

The cytotoxic T lymphocyte antigen 4 (CTLA-4) can bind efficiently to CD80/CD86, thus preventing T-cell co-stimulation via the CD28 pathway. Abatacept (Fig. 1; 7) is a fusion protein of CTLA-4 and the Fc portion of human IgG1 [49]. Abatacept was shown to be effective in the treatment of murine lupus [46] and in patients...
with Rheumatoid Arthritis [50]. However, in two placebo controlled clinical trials of lupus patients (with or without lupus nephritis), Abatacept treatment was not effective as compared to placebo [51]. Thus, currently Abatacept is not approved for lupus treatment, although some clinicians use it as an off label agent.

5. Cytokine blockade targeted treatment

5.1. Tocilizumab (anti IL-6 receptor mAb)

IL-6 is a multifactorial pro-inflammatory cytokine that was shown to play a role in the pathogenesis and treatment of murine lupus [52,53]. Moreover, elevated levels of IL-6 were found in sera of active lupus patients [54]. Tocilizumab (Fig. 1; 8) is a fully humanized mAb against the IL-6 receptor that prevents binding of IL-6 to both, membrane and soluble receptors. A small phase I trial (16 lupus patients) suggested that Tocilizumab is safe and beneficial in SLE [55]. Further controlled clinical studies are required in order to evaluate the therapeutic role of Tocilizumab in lupus. Sirukumab (Fig. 1; 8), a human anti-IL-6 mAb is currently in a phase II clinical study in patients with lupus nephritis (NCT01273389).

5.2. Anakinra (human recombinant IL-1 receptor antagonist (IL-1 Ra))

IL-1 Ra is an endogenous soluble protein that binds IL-1, thus inhibits IL-1 binding to its receptors [56]. Anakinra (Fig. 1; 9), a recombinant IL-1 Ra, was shown to block IL-1 activity and to be beneficial in the treatment of severe Rheumatoid Arthritis patients [56]. Two uncontrolled studies with a small number of lupus patients suggested beneficial effects for Anakinra [57]. Further controlled clinical trials with Anakinra and with the single immunoglobulin IL-1 related receptor (SIGIRR; Fig. 1; 9) that was recently shown to bind both, IL-1 and Toll like receptor 4 (TLR-4) [58], should assess their potential role in the treatment of lupus.

5.3. Interferon alpha (IFN-α) inhibition

Several lines of evidence suggest a major role for type I IFNs (especially IFN-α) in the pathogenesis of murine and human SLE [59,60]. Sifalimumab (Fig. 1; 10), a human IgG1, anti-IFN-α mAb was evaluated in two studies. In the first phase I study, 33 lupus patients were treated with Sifalimumab and 17 with placebo. Sifalimumab treatment resulted in a non-significant clinical improvement without excess of viral infections (compared to placebo) [61]. In the second phase IIa study, Sifalimumab was shown to be safe but without beneficial effects as compared to placebo [62]. Further studies with Sifalimumab (NCT01283139) are currently in progress. Another humanized IgG1 anti-IFN-α mAb, Rontalizumab (Fig. 1; 10), failed to show clinical efficacy over placebo in a phase II study with 238 lupus patients [63]. Nevertheless, in the subgroup of patients with a low IFN signature, Rontalizumab treatment was effective [63]. An additional trial with Rontalizumab (NCT00962832) is currently in progress. Zagrini et al. induced polyclonal anti-IFN-α antibodies in mice and humans by injecting recombinant human IFN-α conjugated to KLH (IFN-α-Kinoid) [64]. The injection of the IFN-α-Kinoid was safe and well tolerated but in spite of the generation of anti-IFN-α antibodies, clinical improvement was not observed [65]. Another approach for IFN-α inhibition is to block its receptor. Currently, two phase II clinical trials with anti-IFN-α receptor monoclonal antibodies are planned.

6. Targeting the complement system

6.1. Eculizumab (Anti-C5 mAb)

The early complement components are essential for immune complex clearance whereas activation of the late components were shown to be associated with lupus exacerbations [66]. Eculizumab is a humanized IgG2/4 mAb directed against the complement protein C5, blocking the formation of the complement terminal membrane attack complex [66,67]. This mAb was shown to ameliorate murine lupus [67]. A phase I trial with Eculizumab in 24 lupus patients demonstrated good safety profile but no clear clinical efficacy [66,68]. To the best of our knowledge there are no current trials with anti-complement agents in lupus patients.

7. Therapeutic approaches for the specific treatment of SLE

The rationale behind attempting the development of antigen specific therapy for lupus as well as for other autoimmune diseases is to achieve the mean that will modulate only the disease specific pathogenic cells and pathways and will leave the rest of the immune system intact. Thus, in contrast to the current standard of care for lupus that suppresses large portions of the immune system, and unlike many of the newly therapeutic approaches that introduce agents that deplete large parts of the targeted cell populations or their function and may cause adverse effects, the antigen specific treatment is aimed at targeting a small cell population that is actually involved in the pathogenesis of the autoimmune disease. Synthetic peptides that are based on sequences taken from antigens that are involved in the pathogenesis of lupus have been studied in a number of laboratories as potential means for targeting specifically lupus associated responses. Below we discuss synthetic peptides that were shown to be tolerogenic T cell epitopes that suppress SLE associated autoimmune responses.

7.1. pConsensus

The tolerogenic peptide designated pConsensus (pCons) is a 15 amino acid long peptide that is based on MHC class I and class II T cell determinants in the V6 region of murine anti-DNA immunoglobulin [69]. Monthly intravenous injections of a high dose (1 mg/ mouse) of pCons to (NZBxNZW)F1 lupus prone mice, before the outbreak of disease, delayed the onset of nephritis, prolonged survival of the treated mice [69] and inhibited the production of lupus associated autoantibodies such as anti-dsDNA, anti-nucleosome, and anti-cardiolipin. In addition, secretion of the pro-inflammatory cytokine, IFN-γ, was diminished [70]. Similar results were observed following treatment of mice with established disease [69]. The tolerogenic effects of pCons were specific to SLE because treatment with the peptide did not interfere with the antibody response to hen egg white lysozyme following the immunization with the latter [69]. As shown for other tolerogenic peptides the mechanism of action of pCons involved the induction of two types of regulatory T cells, namely, peptide-reactive CD4+CD25+Foxp3+ Tregs that suppressed anti-dsDNA autoantibody production in vitro [70], and CD8+Foxp3+ regulatory cells that secreted TGF-β and were shown to suppress anti-dsDNA antibodies in vitro and in vivo [70,71]. pCons induced CD8+ Tregs were resistant to apoptosis and expressed reduced levels of programmed death-1 (PD-1) [72]. Thus, the suppressive capacity of the pCons induced CD8+ cells depended on the intracellular expression of Foxp3 and on the alteration of PD1 on the cell surface. A single transfer of the CD8+ inhibitory cells to irradiated (NZBxNZW)F1 recipients down-regulated disease manifestations of the recipient mice [71]. Further studies led to the conclusion that pCons induced...
CD4+ Tregs suppress autoimmune responses in a p38MAPK-dependent fashion [73]. In addition, the threshold for T effector suppression by Tregs in (NZBxNZW)F1 mice was reported to be lowered by pCons in a p38-independent fashion [74]. The above data suggest that different pathways are affected by pCons.

The effects of pCons were also tested in vitro on peripheral blood mononuclear cells (PBMC) of SLE patients. Incubation of PBMC of SLE patients but not of healthy controls in the presence of pCons resulted in the expansion of CD4+CD25+ Tregs. The latter induction was FoxP3 for cell contact-mediated suppression of proliferation and IFN-γ production in target CD4+CD25+ T cells. The induction of FoxP3 in SLE Treg cells was observed only in seropositive and not in seronegative patients [75]. Thus, the up-regulation of functional CD4+ Treg was shown in PBMC of SLE patients as was previously shown in SLE-afflicted mice. No clinical trials have been reported for pCons.

7.2. Nucleosomal peptides

Nucleosomes were reported to play a major role in the pathogenesis of murine and human lupus [76,77]. Five peptides in nucleosomal histones were demonstrated to be dominant autoepitopes, recognized by autoimmune T helper as well as B cells of lupus affected mice and of human patients. These peptides (H172, H2B9, H3, H46-29, and H41-94) that were derived from a highly conserved, ubiquitous self-antigen can be promiscuously presented in the context of diverse MHC class II alleles [76,77]. Tolerance induction with high dose of the peptides delayed disease development in prenephritic (SWRxNZB)F1 (SNF1) mice and prolonged survival of old SNF1 mice with established glomerulonephritis [78]. Furthermore, subcutaneous administration of a very low dose (1 mg/mouse every 2 weeks) of the peptides diminished autoantibody levels, delayed kidney damage and prolonged life span of the treated SNF1 mice. The histone epitope H471-94 was the most effective in inducing low zone tolerance because it suppressed autoimmunity to other pathogenic epitopes and to whole nucleosomes (tolerance spreading) [78,79]. Peptide H471-94 suppressed lupus associated autoimmune responses by a mechanism that involved dendritic cells (DC), especially plasmacytoid DC (pDC) that, upon interaction with the peptide, expressed a tolerogenic phenotype, produced increased amounts of TGF-β and diminished IL-6 [80]. The tolerogenic DC blocked SLE manifestations in SNF1 mice by the induction of autoantigen specific CD4+CD25+ and CD8+ regulatory T cells [79] associated with the suppression of inflammatory Th17 cells that infiltrate the kidneys of untreated lupus mice [80]. The peptide induced Tregs could also block accelerated disease upon adoptive transfer into lupus afflicted mice [79]. It is noteworthy that suppression by the H471-94 induced Treg was demonstrated to be preferentially directed against lupus associated autoimmune responses and did not affect immune responses to foreign antigens [79,80].

The potential effects of the nucleosomal histone peptide epitopes, on human patients, were assessed by an in vitro assay in which PBMC were cultured in the presence of low doses of the histone peptides [81]. It was demonstrated that CD4+CD25+FoxP3+ or CD4+CD45RA+FoxP3+ T cells, and CD8+CD25+FoxP3+ T cells were induced in PBMC from inactive lupus patients and from healthy controls. However, induction of conventional Tregs by the peptides in PBMC of active patients was less efficient. The peptide induced Tregs required TGFβ/ALK/S/pSmad 2/3 signaling, and they expressed the TGF-β precursor, latency associated peptide. Moreover, the peptide induced Tregs suppressed IFN-γ gene expression by PBMC of lupus patients. Finally, the histone peptides suppressed autoantibody production by PBMC from active lupus patients. Because Tregs induction in PBMC of active patients was not efficient, it was suggested that low dose administration of the histone peptide epitopes suppressed lupus autoimmune responses by mechanisms other than Treg induction [81]. No in vivo clinical trials have been reported with any of the nucleosomal histone peptide epitopes.

7.3. P140

One of the peptide based therapeutic means under development for the treatment of lupus is the 21-mer peptide (131–151) of the U1-70K small nuclear ribonucleoprotein (snRNP) which is a major spliceosomal autoantigen recognized in SLE. Peptide 131–151, the sequence of which is fully conserved between the mouse and human, was found to be recognized early during the progression of the disease by IgG antibodies and CD4+ T cells from both MRL/lpr and (NZBxNZW)F1 lupus prone mice [82]. However, only the peptide analog that contains a phosphoserine residue at position 140 and has been named P140, was capable of ameliorating the clinical manifestations of lupus in treated MRL/lpr mice [83]. Thus, intravenous administration of P140 to young MRL/lpr mice reduced the anti-DNA autoantibody production, delayed the development of proteinuria and significantly prolonged survival of the treated mice [83]. P140 peptide was shown to be a promiscuous MHC bound, as shown in studies with various murine MHC molecules and with a large panel of HLA class II molecules [84]. Incubation of peripheral blood lymphocytes (PBLs) of SLE patients with P140 resulted in the secretion of IL-10 in the cell cultures without proliferation of CD4+ T cells suggesting that P140 is an immunomodulatory peptide. The effect of P140 was suggested to be specific because the recognition of P140 by T cells from patients with other autoimmune diseases or with infectious diseases could not be demonstrated [85]. Furthermore, repeated administrations of P140 into MRL/lpr mice transiently abolished T cell reactivity to other regions of the U1-70K protein and to epitopes from other spliceosomal proteins without affecting the ability of the treated mice to mount an anti-viral immune response [86]. The latter results suggest that tolerance spreading [78] plays a role in the mechanism of action of P140. Epitope spreading is a process in which epitopes that are distinct from an inducing epitope become major targets in an ongoing immune response and more specifically in an autoimmune process [87]. In the case of P140 it has been shown in MRL/lpr mice that the RNP1 motif initiated the spreading of the immune response to the whole U1-70K protein (intramolecular spreading) and that an immune response induced against the RNP1 motif can proceed to other spliceosomal proteins that may or may not contain an RNP1 motif but are localized in the same particle (intramolecular spreading) [86]. It appears that treatment of SLE-prone mice with P140 peptide resulted in the down-regulation of autoreactive T- and B-cell responses to other self-antigens associated with lupus (tolerance spreading).

The mechanism of action of P140 has not been completely elucidated yet, however, it appears to differ from those reported for other tolerogenic peptides developed for the treatment of SLE. Upon administration of P140 peptide to MRL/lpr mice the peptide was found to interact selectively with the constitutive heat-shock HSC70/Hsp73 chaperone protein, which is present on a majority of immune cells [88]. HSC70 was shown to play an important role in the presentation of peptides to MHC molecules, both as chaperone to MHC molecules [89] and in the autophagy process [90]. After binding of P140 to HSC70, the autoantigen processing by the antigen presenting B cells of MRL/lpr mice might be down-regulated leading to a decrease of autoreactive T cell priming and signaling via a mechanism involving a lysosomal degradation pathway [91]. A previous report suggested that the P140-HSC70 complex activates γδ T cells. By a granzyme-B and caspase-dependent
mechanism, apoptosis of T and B cell lymphocytes was induced in the MRL/lpr mice through a regulatory circuit that involves the γδ T cells [88]. P140 also down-regulated the expression of programmed death 1 (PD1/CD279) which is overexpressed at the surface of MRL/lpr CD4+ T cells [88]. Thus, the mechanism underlying the immunomodulating effects of P140 appears to involve various cell types and pathways that are not fully understood yet.

The first clinical trial with the P140 peptide (IPP-201101, Lupu- zor) was conducted in two centers and was aimed at assessing the safety, tolerability and efficacy of the peptide in an open-label, dose escalation study of 20 patients with moderately active SLE. Patients who received a low dose of P140 (200 μg at weeks 0, 2 and 4) showed an improvement in PGA and SLEDAI score. A higher peptide dose (1 mg given 3 times) was less effective than the 200 μg dose. No clinical or biological side effects were observed in the patients, except for some local irritation at the high concentration [92].

Phase IIb clinical trial with P140/Lupu-zor was a double-blind, placebo controlled study of SLE patients in Europe and Latin America. Patients (149), with a >8 SLEDAI-2K score, who did not have an A score on the BILAG-2004 index, were randomly assigned to receive 200 μg of the peptide subcutaneously either every 4 weeks or every 2 weeks in addition to standard of care. The study lasted for 24 weeks. The results of the trial indicated that the 200 μg dose of P140 administered every 4 weeks was statistically superior to placebo. The difference between the group that received the peptide every 2 weeks and the placebo group did not reach statistical significance. The peptide was generally well tolerated with no significant drug-related adverse events [93]. It has been reported that the FDA has approved P140/Lupu-zor for the performance of a Phase III clinical trial.

7.4. hCDR1

Loss of self-tolerance is one of the main characteristics of lupus as well as of other autoimmune diseases. Therefore, a potential specific therapeutic approach for SLE is the development of a mean that will restore immune tolerance to lupus associated immune responses. We have previously demonstrated high homology between the variable regions coding for the heavy and light chains of anti-DNA monoclonal antibodies isolated from mice with induced experimental SLE and from the SLE-prone (NZBxNZW)F1 mice [94]. We then hypothesized that the conserved regions of the pathogenic autoantibodies might be of importance in the induction and progression of lupus. Therefore, we synthesized and characterized two peptides that were designed based on the complementarity determining regions (CDRs) of a pathogenic murine monoclonal anti-DNA antibody (SG12) that bears the major ideotype designated 16/6Id [95]. The two peptides based on CDR1 and CDR3 of the murine anti-DNA autoantibody were found to either prevent [96,97] or treat an already established SLE-like disease in mice [97,98]. The beneficial effects of the treatment were manifested in the reduction of SLE associated antibodies and in the down-regulation of clinical symptoms including kidney damage [96–98].

As a potential candidate for the specific treatment of SLE patients we have further designed and synthesized a 19 mer tolerogenic peptide designated hCDR1 [99] which is based on the sequence of the heavy chain CDR1 of a human monoclonal anti-DNA antibody [100] that expresses the 16/6Id [101]. Administration of small doses (25–50 μg) of hCDR1 subcutaneously once a week for 10–14 weeks resulted in a significant amelioration of the serological (reduced autoantibody production) and clinical (decreased renal damage and brain pathology) manifestations developed either in SLE-prone mice or in mice with experimental SLE that was induced following immunization with the monoclonal anti-DNA, 16/6Id expressing antibody [102–104]. Similarly, severe combined immunodeficient (SCID) mice that were engrafted with peripheral blood lymphocytes from SLE patients and developed SLE manifestations benefited from the treatment with hCDR1 [105].

The beneficial effects of hCDR1 were associated with reduced production and expression of inflammatory cytokines (e.g. IL-1β, IFN-α, IFN-γ, IL-10, TNF-α) and up regulation of the immunosuppressive cytokine TGF-β [102,106]. We have further shown an aberrant control of the IFN-γ signaling. Thus, the mRNA and protein levels of the negative regulator, suppressor of cytokine signaling (SOCS)-1, were diminished whereas the levels of the IFN-γ receptor downstream molecule phosphorylated signal transduction and activator transcription (pSTAT)-1 were elevated in spleen-derived cells of SLE-afflicted mice. Treatment with hCDR1 up-regulated SOCS-1 and restored the control of IFN-γ signaling pathway in association with clinical amelioration [107].

Treatment with hCDR1 was shown to down-regulate (via up-regulation of TGF-β and reduction of pERK) two adhesion and costimulatory molecules, LFA-1 and CD44, which are important for T cell-antigen presenting cell (APC) interaction [108]. Further, following its binding to MHC-class II hCDR1 inhibited T cell receptor signaling by up-regulating two negative regulators of T cell activation, namely, Foxp1 and Foxo3a, resulting in the inhibition of NF-κB accumulation and IFN-γ production [109]. In addition, treatment with hCDR1 up-regulated a pair of transcription factors, early growth response (EGR)-2 and EGR-3, which are required for the induction of anergy in association with the inhibition of AKT phosphorylation [110].

A central mechanism of peripheral tolerance involves the active suppression of autoimmune responses by T cells with regulatory capacity [111]. The induction of T regulatory cells (Tregs) plays a key role in the mechanism of action of hCDR1. Treatment with hCDR1 up-regulated CD4 Tregs by 30–40%. The hCDR1-induced CD4+ Tregs expressed the characteristic markers of regulatory cells such as CD45RBlow, cytotoxic T lymphocyte antigen (CTLA)-4 and Foxp3 [112]. In addition, the survival molecule Bcl-xl was up-regulated in CD4 Tregs of tolerized mice and was shown to be of importance for the development and function of CD4 Tregs [113]. The adoptive transfer of enriched hCDR1-induced CD4 Tregs into SLE-afflicted mice resulted in a significant amelioration of the serological and clinical manifestations. Depletion of Tregs diminished significantly the therapeutic effects of hCDR1 whereas administration of Treg enriched populations was beneficial to the diseased mice [112]. Treatment with hCDR1 also induced Foxp3-expressing CD8+ CD28- Tregs [114]. The in vivo effects of hCDR1-induced CD8 Tregs, upon their adoptive transfer into SLE affected mice, were limited and significantly less prominent than those of hCDR1 induced CD4+ Tregs. Nevertheless, in vivo depletion of CD8+ cells diminished the clinical improvement following treatment with hCDR1. Thus, CD8+ Tregs were demonstrated to be required for the optimal expansion, development and inhibitory function of hCDR1-induced CD4+ Tregs [114].

The treatment of mice with hCDR1 also reduced the rate of T cell apoptosis. Several signaling pathways for apoptosis were affected by hCDR1: 1) The c-Jun NH2-terminal kinase (JNK) that is part of the p21ras/MAP kinase pathway and is highly expressed in T cells of SLE-affected mice was significantly diminished following hCDR1 treatment [115]. 2) The Fas signaling pathway was also affected by treatment with hCDR1. Thus, CD4 Tregs from hCDR1 treated mice repressed Fas signaling via the down-regulation of the expression of Fas ligand in a CTLA-4-dependent manner, and diminished the activity of caspase 8 and 3 and up-regulated the survival molecule Bcl-xl [116–118]. 3) Finally, the elevated expression of Bcl-xl in T cells of hCDR1 treated mice led to a diminished rate of T cell apoptosis and activation. It is noteworthy that hCDR1-induced CD4 Tregs elicited the expression of Bcl-xl in effector T cells and that

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Bcl-xL was involved in inducing the regulatory/inhibitory molecules Foxp3, CTLA-4 and TGF-β and in suppressing PD-1 [113]. The effect of hCDR1 on T cells, including the induction of functional CD4+ and CD8+ regulatory T cells and the down-regulation of the elevated T cell apoptosis, played a critical role in the mechanism by which hCDR1 ameliorated lupus manifestations.

hCDR1 was also demonstrated to affect other cell populations that play a role in the pathogenesis of lupus. Dendritic cells (DC) of lupus afflicted mice and patients were found to display an aberrant phenotype with higher expression of the maturation markers, namely, MHC-class II, CD80 and CD86, and elevated production of pro-inflammatory cytokines including IL-12 [119]. Treatment with hCDR1 lowered the expression levels of the latter on the DC. Thus, treatment with hCDR1 induced DC with an immature/tolerogenic phenotype that suppressed T cell proliferation and activation [120] leading to the expansion of regulatory T cells.

B cells play an important role in the pathogenesis of SLE. They produce autoantibodies, function as antigen presenting cells and produce soluble mediators that are involved in the initiation and perpetuation of the inflammatory process [121]. BAFF, also known as BlyS, is a member of the TNF superfamily that regulates B-cell survival and autoreactivity [122]. Serum levels and gene expression of the human and murine BAFF were significantly increased in lupus patients as well as in murine models of lupus [42]. BAFF production was reduced in hCDR1-treated mice in association with diminished production of dsDNA-specific autoantibodies, proteinuria and IFN-γ and IL-10 that induce BAFF secretion. The reduced levels of BAFF correlated with a lower rate of maturation and differentiation of B cells and with a decrease in anti-apoptotic gene expression by B cells resulting in their higher apoptotic rate. Moreover, signaling through the NF-κB pathways was shown to be involved in the inhibition of BAFF by hCDR1 [123].

An additional pathway regulating B-cell survival is controlled by the macrophage migration inhibitory factor (MIF) and its receptor CD74 [124,125]. B cells from (NZBxNZW)F1 SLE afflicted mice over-express CD74, CD44 and MIF which binds to their complex. The induction of the CD74/MIF pathway in B cells of SLE-diseased mice is associated with increased B cell survival. Treatment of SLE affected mice with hCDR1 resulted in diminished expression of the CD74/CD44 complex along with the down-regulation of MIF, the ligand of this complex. As in the case of the BAFF pathway a reduction in survival molecules and in B cell survival was demonstrated [126]. It is noteworthy that up-regulation of CD74 and CD44 expression was detected in two target organs of SLE, namely, brain hippocampi and kidneys of the diseased mice. Treatment with hCDR1 diminished the expression of those molecules to the levels determined for young healthy mice, in association with an observed clinical improvement [126].

The therapeutic effects of hCDR1 were also assessed in lupus afflicted pigs in which the disease was induced following immunization with the monoclonal anti-DNA autoantibody, 16/6Id [127]. Weekly treatment injections (for 10 weeks) with hCDR1 led to clinical improvement, diminished expression of the pathogenic cytokines (e.g. IL-1β), TNF-α, IFN-γ and IL-10 and elevated expression of TGF-β, the anti-apoptotic molecule Bcl-xL and the suppressor master gene, Foxp3 [127] similarly to effects observed in the various murine models that were treated with hCDR1.

In vitro experiments were performed to test the effects of hCDR1 on human PBMC from SLE patients. Incubation of hCDR1 with PBMC of patients resulted in a significant down-regulation of IL-1β, IFN-α, IFN-γ and IL-10 gene expression. The anti-apoptotic molecule Bcl-xL was up-regulated and caspase-3 was diminished resulting in reduced T cell apoptosis. Furthermore, hCDR1 increased the expression of TGF-β leading to the expansion of CD4+CD25+FoxP3+ functional Tregs [106,128]. These results suggested that hCDR1 immunomodulated PBMC of lupus patients via mechanisms similar to those observed in murine lupus models.

An important aim in the treatment of lupus as well as any other autoimmune diseases, is to suppress the SLE related autoimmune responses and, at the same time, to spare the normal function of the immune system. In agreement, it has been previously shown that hCDR1 inhibited in vitro murine and human T cell proliferation as well as IFN-γ and IL-2 production only in cases of lupus associated responses and did not affect responses to unrelated antigens [99,108,109,110]. Similarly, the inhibitory effects of hCDR1 on the expression of IFN-α was shown to be specific to lupus and did not affect healthy controls and patients with primary anti-phospholipid syndrome [106]. Further, hCDR1 treatment of SLE-like disease in SCID mice, transplanted with PBMC of SLE patients, led to the suppressed production of human anti-dsDNA autoantibodies in association with the amelioration of disease manifestations. However, no significant effects could be observed on the levels of human anti-Tetanus Toxoid antibodies [105]. Finally, only Tregs induced by hCDR1 ameliorated disease manifestations when transferred into SLE afflicted mice. Tregs originating from a specific peptide or from vehicle treated mice did not have a significant clinical effect on mice with established lupus [112]. The specific effect of hCDR1 was further confirmed by the fact that hCDR1 induced functional Tregs were not capable of inhibiting Myasthenia Gravis associated responses (Mozes E. et al., unpublished results).

Two placebo controlled phase I clinical trials, single dose (Ja-36 patients) and a one month long multiple (8) dose (1b-33 patients), were conducted with hCDR1 (Edratide™) by Teva Pharmaceutical industries, Ltd and showed good safety profile and tolerability. A randomized, double-blind, placebo-controlled phase II clinical trial (PRELUDE) was further conducted by Teva with hCDR1 (Edratide™). 340 patients from 12 countries with SLEDAI-2K index of 6–12 were recruited. Treatment was weekly subcutaneous administration of Edratide at doses of 0.5, 1.0, 2.5 mg or placebo. Edratide was safe and well tolerated. The primary endpoint of SLEDAI-2K was not met. However, a number of the secondary BILAG score results demonstrated significant beneficial effects. Thus, a higher number of substantial BILAG responders, in the 0.5 mg Edratide/week treated patients, was observed in the whole group (36%vs.22%, p = 0.03) and more so in patients on low dose (<20 mg prednisone equivalent/day) or no steroids (40%vs.19%, p = 0.007 and 54%vs.13%, p = 0.05, respectively). Similar positive trends (46%vs.26%, p = 0.05) were identified when only seropositive patients were analyzed [129]. Further studies using an alternative endpoint in seropositive SLE patients and implementing strict steroid treatment algorithms are planned.

The effect of in vivo treatment with hCDR1/Edratide on the various cytokines and molecules shown to be involved in the mechanism of action of the peptide was analyzed. The expression of the various genes was determined in mRNA isolated from blood samples of a limited number (9) of patients that participated in the PRELUDE study. Treatment with hCDR1/Edatide for 24 weeks diminished the mRNA expression of IL-1β, TNF-α, IFN-γ, IFN-α and IL-10 and of the pro-apoptotic molecules caspase-3 and caspase-8 [106,130]. In addition, BlyS expression was significantly inhibited by the in vivo treatment with hCDR1. Of note, the BlyS inhibitor (Belimumab) has been approved for the treatment of SLE patients in 2011 [40]. In contrast to the down-regulation of the lupus associated pathogenic molecules, in vivo treatment with hCDR1 up-regulated the expression of both, TGF-β and Foxp3. The observed effects on the various gene markers correlated with a significant decrease in SLEDAI-2K and BILAG scores in the hCDR1 peptide treated as compared to the placebo treated patients [130]. Thus, the beneficial effects of hCDR1/Edratide on SLE patients are

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via a mechanism similar to that demonstrated for murine models of lupus.

Fig. 2 illustrates the mechanism of action of hCDR1 that leads to the amelioration of lupus manifestations in mice as well as in SLE patients: The interaction of hCDR1 with APC/DC results in the induction of tolerogenic DC with down-regulated expression of MHC class II and of the costimulatory molecules CD80/CD86, and diminished production of the pathogenic cytokines (e.g. IL-6 and IL-12). When presented to the autoreactive T cells by the tolerogenic APC, hCDR1 induces two subsets of Tregs, namely, CD8+ and CD4+ Tregs that express Foxp3 and inhibitory molecules (e.g. TGF-β, CTLA-4). The functional Tregs induce inhibitory molecules in the effector (cytotoxic/helper) T cells. The suppressed activity of effector T cells contributes to the reduced secretion of pathogenic cytokines. BAFF/BLyS production by the suppressed cell populations is diminished as well. In the B cell compartment, the suppressed T cell helper activity and the down-regulated BAFF/BLyS production result in reduced B cell maturation and differentiation, up-regulated B cell apoptosis, and suppressed B cell activation and autoantibody production. These effects of hCDR1 culminate in the improvement of the serological and clinical manifestations of SLE.

7.5. Characteristics and effects of the various peptides developed for the treatment of SLE

Table 1 summarizes the information available on the four peptides that were studied the most for their ability to suppress lupus manifestations. The common denominator for these 4 peptides is their being tolerogenic T cell epitopes that down-regulate specifically lupus associated autoimmune responses. All peptides are sequences of conserved regions of molecules that are known to be involved in the pathogenesis of lupus. It should be noted that three of the peptides (H471-94, P140 and hCDR1) were shown to bind to a variety of MHC class II alleles. Further, treatment with the peptides resulted in tolerance spreading because they down-regulated autoimmune responses to lupus associated epitopes and antigens other than the tolerance inducing peptides. Because of their SLE specific effects the peptides do not deplete or affect large cell population; in fact they immunomodulate cell types and pathways that are involved in the pathogenesis of lupus and by a cascade of events restore the normal immune response. As seen in Table 1 for some of the peptides the mechanism of action has been studied more thoroughly than for the others, nevertheless, it appears that all peptides induce their beneficial effects via a number of pathways. For 3 of the peptides, namely, pCONS, H471-94 and hCDR1, CD4 and CD8 regulatory T cells have been reported to play a key role in their mechanism of actions. The latter peptides were also shown to bind to MHC class II for their presentation to the T cell. Both, H471-94 and hCDR1 were reported to induce tolerogenic DC upon their interaction with these cells. Thus, the effects of the peptides is upstream the immune system. P140 peptide appears to function via a different mechanism. It was reported to interact first with heat-shock HSC70, however it also induced a regulatory circuit that led to down-regulation of SLE manifestations. The two peptides that were tested in clinical trials (P140/Lupuzor, and hCDR1/Edratide) were reported to be safe and well tolerated. Thus, synthetic peptides are attractive potential means for the specific and safe treatment of lupus patients.

8. Conclusions

The major progress made in recent years towards the understanding of the pathogenesis and development of SLE resulted in attempts to develop novel biological agents for the treatment of the disease. In this review we discussed a variety of biological therapies that are under different stages of development. The latter target different cell populations and molecules either by their depletion or by blocking inflammatory processes. Indeed, one of these biological agents, namely, Belimumab, that targets BLyS, has been the first drug to be approved by the FDA for the treatment of SLE patients. However, in spite of the fact that the newly developed biological agents target cells and molecules that are involved in the pathogenesis of SLE they are not lupus specific and may affect the normal immune system as well resulting in various infections in part of the treated patients. Attempts to develop therapeutic means that immunomodulate only the SLE associated autoimmune
Table 1  
Characteristics and effects of peptides developed for SLE treatment.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Origin</th>
<th>Mechanism of action</th>
<th>Effects in experimental SLE</th>
<th>Effects in human SLE</th>
<th>Clinical trial status</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCONS</td>
<td>Synthetic murine anti-dsDNA mAb</td>
<td>↓ IFN-γ, IL-4, ↑ CD4 Tregs, CD8 Tregs</td>
<td>↓ Anti-dsDNA, anti-nucleosome, anti-cardiolipin Delayed onset of nephritis Prolonged survival</td>
<td>↑ CD4 Tregs</td>
<td>N/A</td>
<td>[69–75]</td>
</tr>
<tr>
<td>Nucleosomal peptides</td>
<td>Nucleosomal histones</td>
<td>↓ IFN-γ, IL-10, IL-6, ↑ Th17, ↑ TGF-β</td>
<td>↓ Anti-dsDNA, anti-nucleosome, anti-cardiolipin Delayed onset of nephritis Prolonged survival</td>
<td>↑ CD4 Tregs, CD8 Tregs, ↑ IFN-γ, ↑ IL-10, ↑ IL-6 Induction of tolerogenic DC</td>
<td>N/A</td>
<td>[76–81]</td>
</tr>
<tr>
<td>P140 (LUPUZOR)</td>
<td>Phosphorylated analog of the U1-70K snRNP</td>
<td>Interacts with heat-shock HSC70/HSP73, ↓ Processing by antigen-presenting B cell, ↑ Regulatory circuit that involves γδ cells</td>
<td>↓ Anti-dsDNA, anti-nucleosome, anti-cardiolipin Delayed onset of nephritis Prolonged survival</td>
<td>↑ IL-10, ↑ Activated CD4+ Open-label dose escalation study (20 patients), Phase IIb-double blind (149 patients), Phase III clinical trial planned</td>
<td></td>
<td>[82–86,88,91–93]</td>
</tr>
<tr>
<td>hCDR1 (Edratide)</td>
<td>Based on CDR1 of a human anti-DNA mAb</td>
<td>↓ IL-1β, IFN-γ, ↑ IL-10, ↑ IFN-γ, ↑ IL-6, ↑ TGF-β, ↑ SOCS-1, ↓ T cell apoptosis, ↓ B cell apoptosis, ↑ BAFF Induction of tolerogenic DC</td>
<td>↓ Anti-dsDNA, anti-nuclear Abs, anti-cardiolipin Amelioration of renal and CNS manifestations Prolonged survival</td>
<td>↓ IL-1β, IFN-γ, ↑ IL-6, ↑ IFN-γ, ↑ TNF-α, ↑ TGF-β, ↑ BLyS, ↓ B cell apoptosis, ↑ T cell apoptosis, ↑ BAFF Induction of tolerogenic DC, ↑ CD4 Tregs, CD8 Tregs, ↓ T cell apoptosis, ↓ B cell activation</td>
<td>Double-blind: Phase Ia (36 patients), Phase Ib (33 patients), Phase IIa (340 patients), Phase IIb clinical trial planned</td>
<td>[94–100,102–110,112–118,120,123,126–130]</td>
</tr>
</tbody>
</table>
responses without affecting any other functions of the immune system led to the synthesis of lupus specific tolerogenic peptides (such as hCDR1). These peptides were studied for their mechanism of action and effects on SLE manifestations. The tolerogenic peptides exhibit their effects on various cell types and immunological pathways that are involved in the pathogenesis of lupus, they suppress only SLE related autoreactive responses without interfering with normal immune functions and those tested in SLE patients (P140 and hCDR1) were reported to be safe and well tolerated. Thus, tolerogenic peptides appear to be attractive candidates for the specific treatment of lupus and further attempts towards their development are likely to be rewarding.

This review was written to honor professors Michael Sela and Ruth Arnon. This issue is part of dedicated themes in the Journal of Autoimmunity that recognize unique contributions and unique problems that have greatly advanced basic research and its therapeutic implications. Previous honorees have included Noël Rose, Ian Mackay, Chella David, Abul Abbas and Pierre Youinou. Arnon has been a dear colleague and friend for many years and I reward my use in Immunology and Autoimmunity research. Prof. Arnon Arnon has been a dear colleague and friend for many years and I submitted an article to this issue in recognition of the significant contributions of Drs. Sela and Arnon to the field of Immunology and Autoimmunity and their outstanding important achievement of being first to develop a therapeutic mean (Copazone) that is based on a synthetic polymer and has by now impacted a large number of patients with the autoimmune disease, Multiple Sclerosis.

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