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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]. Dysregulation of both, the innate and the adaptive immune systems play a role in SLE with the production of variety of autoantibodies and pro-inflammatory cytokines, impaired T cell function and enhanced apoptosis [1–3]. The clinical spectrum of lupus varies, ranging from mild mucocutaneous/musculoskeletal manifestations to life-threatening renal or neurologic disease [1,2]. Disease activity and lupus organ involvement fluctuate along the time with flares and remissions (either spontaneous or induced by treatment) [1,2]. Although the precise etiology of SLE is not fully defined yet, genetic, hormonal and environmental factors appear to play a role in the pathogenesis and course of the disease [3,4].

The current "standard" treatment of SLE includes anti-malarial agents (mainly Hydroxychloroquine, HCQ), corticosteroids, immunoglobulins (IVIG) and cytotoxic immunosuppressive agents [1,2,5]. HCQ was shown to be effective in the treatment of mild to moderate mucocutaneous and musculoskeletal manifestations of lupus [5]. Corticosteroids, given orally or intravenously, are effective for almost all lupus related manifestations. However, the long-term adverse effects of the latter agents limit their usage. Recently, Thamer et al. demonstrated that a dose of as low as 6 mg prednisone per day increases the corticosteroids-induced organ damage by 50% [6]. Thus, a steroid sparing therapeutic approach is mandatory [7]. Other immunosuppressive agents such as Cyclophosphamide, Azathioprine, Methotrexate and Mycophenolate Mofetil were shown to be effective in the treatment of moderate to

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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

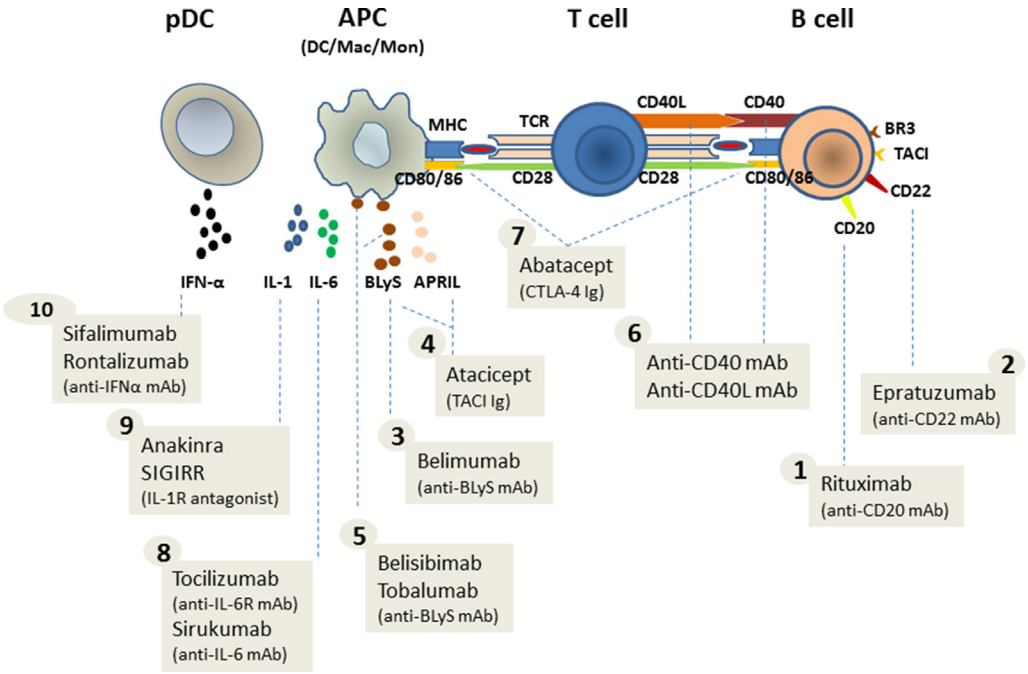

Fig. 1. Biological treatments for SLE: Targets and mode of action. The numbers of the therapeutic agents are as designated in the text. pDC – plasmacytoid DC; Mac – macrophages; Mon – monocytes.