

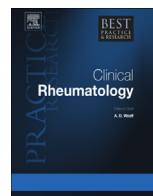


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New therapeutic avenues in SLE



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Although the use of corticosteroids and immunosuppressive agents such as cyclophosphamide and mycophenolate has led to reduced mortality in systemic lupus erythematosus (SLE), there is a need for development of new biologic agents to improve outcomes further. The pathogenesis of SLE involves many components of the immune system, notably B cells, T cells, cytokines and innate immunity, which are potential targets for the new biologic therapies. In this study, the rationale for the development of new therapies in SLE and the progress that has been made in each direction of therapy are described. Most progress has been made with agents directed against B cells, especially rituximab and belimumab and the latter has been the subject of two successful randomised clinical trials (RCTs). Anti-T-cell and anti-cytokine therapies are further back in the development process, but promising advances can be anticipated over the next decade.

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Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune rheumatic disease that can affect every organ system. The disease is characterised by deposition of autoantibodies and immune complexes, leading to widespread tissue damage. Over the last half century, the 5-year survival rate of patients with SLE has improved significantly from <50% in the 1950s to >90% more recently [1]. Despite this, there is still an increased risk of mortality compared to the general population [2]. The use of corticosteroids revolutionised the treatment of SLE in the 1950s and remains the mainstay of treatment but carries with it multiple long-term side effects contributing to disease morbidity. Unlike the targeted biological therapies that have been propelled to the forefront of disease management in rheumatoid arthritis (RA), the movement in SLE has been at a much slower pace. The mortality from lupus nephritis has improved in the last 30 years, but the improvements have slowed with virtually no difference in outcome observed in the last decade compared to the one before [3], thereby suggesting that we may have reached the limits of current therapy. Therefore, there is a clear void to fill in the development of targeted biological therapy in SLE. Developing an increasing understanding of the complex pathophysiology of SLE is pivotal for the development of new drugs targeting the key molecules in disease pathogenesis. The key biological agents are studied in association with the targeted immunological pathways and the key trial data are summarised (see Fig. 1).

Rationale for targeting B cells in SLE

B cells are proposed to play a central role in the pathogenesis of SLE with B-cell hyperactivity and loss of tolerance being hallmarks of this process. The failure in check points peripherally and centrally (within the bone marrow) results in the loss of B-cell tolerance, which occurs early in disease [4]. Defects in apoptosis, resulting in an abnormal programmed cell death, have been demonstrated in SLE. An increased apoptotic rate in lymphocytes is accompanied with an impaired clearance of the apoptotic material. Macrophages from patients with SLE have been shown to engulf less apoptotic material in vitro compared to those from the healthy controls [5]. This apoptotic material includes blebs consisting of cellular material exposed on the surface of dying cells during apoptosis and incorporating antigens that are normally intracellular. Thus, the failure of macrophages in removing this material implies that these antigens are exposed to the immune system, leading to the activation of innate immune cells and the B-cell receptor (BCR) of autoreactive B cells, leading to B-cell activation and expression of the B-cell survival molecule receptor (BAFF) and APRIL (a proliferation-inducing ligand) [6]. BAFF and APRIL, cytokines of the tumour necrosis factor (TNF) ligand family, are thought to play a pivotal role in the development and maintenance of SLE [7].

Polyclonal B-cell activation results in the production of autoantibodies directed against many nuclear, cytoplasmic and plasma membrane antigens. At least 95% of the SLE patients have anti-nuclear antibodies (ANAs). Many of the clinical manifestations of lupus result from an immune complex deposition in tissues and subsequent multi-organ damage. The immune complexes are formed as anti-nuclear antibodies that bind to the nuclear material. B cells also perpetuate the inflammatory response by presenting autoantigens to T cells and producing pro-inflammatory cytokines [8].

Many B-cell-based therapies have been developed with the ongoing clinical trials. Some of the B-cell-targeted therapies have been tested in clinical trials in lupus have been reviewed.

Rituximab

Rituximab is a chimeric monoclonal antibody against CD20, a surface molecule present on pre-B and mature B cells. The drug was approved for use in RA in 2006 by the Food and Drug Administration and has been used off-label in the treatment of SLE patients with refractory disease [9]. The first open uncontrolled study of rituximab for SLE patients was published by Professor Isenberg's group at the University College London, which showed improvements in the clinical and laboratory features, and [10] these findings were replicated in many similar uncontrolled studies [11]. However, disappointingly two phase III randomised controlled trials (RCTs) involving patients with moderate to severe lupus (EXPLORER) and patients with class III or IV lupus nephritis (LUNAR) did not meet their primary

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