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New biologic therapy for systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a heterogenous multisystemic autoimmune disease that is associated with considerable morbidity and mortality. Rituximab is one of the earliest biologic therapies used in SLE. It performed well in off-label studies but failed to demonstrate efficacy in randomised controlled trials. Abatacept is a biologic developed for inflammatory arthritis but has shown promise in SLE. Belimumab is the first biologically approved therapy in fifty years for treatment of SLE. The development of biological therapies for SLE parallels the increasing understanding of the immunopathogenesis of SLE and looks promising. New drugs in development are those targeting the co-stimulatory modulation, cytokines and the B and T cells. Of interest are epratuzumab, the interferon antagonists and peptide-based therapies.

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Introduction

Systemic lupus erythematosus (SLE) is a complex multisystemic autoimmune disease caused by a dysregulated immune system leading to autoantibody production [1].

Considerable progress has been made in our understanding of the pathogenesis of SLE but the mainstay of therapy has, for the past fifty years or so, been hydroxychloroquine, corticosteroids and immunosuppressants [2]. Biological therapies have been used successfully in the treatment of rheumatoid arthritis (RA) for more than 20 years but this type of therapy has been slow to take off in SLE. The sheer heterogeneity of clinical presentations and immunopathogenesis of SLE, coupled with difficulties with trial design and the lack of reliable biomarkers, has been a hurdle to the development of biologics in SLE [1].

March 9th 2011 was an exciting date for rheumatology because it marked the approval of belimumab, a B lymphocyte stimulator (BLyS) inhibitor, the first licensed therapy in fifty years for lupus, by the US Food and Drug Administration. On the basis of increased understanding of the immunopathology of SLE, many new targeted therapies are being investigated as potential therapies for SLE. This review will summarise drugs that are already in use and those that are still in development (see Figure 1).

Pathogenesis of SLE

SLE has been considered in the past as a disease characterised by a dysregulated adaptive immune response, involving T-cell and B-cell abnormalities that result in the formation of new autoantibodies [1]. However, growing evidence implicates dysregulation of innate immunity as well, with dendritic cells, neutrophils and macrophages contributing to disease pathogeneses [3] (see Figure 1). An increasing array of cytokine abnormalities has been implicated in the pathogenesis of SLE, either as part of the pathogenetic core process of lupus or as secondary markers reflecting immune dysregulation [3]. The accompanying figure summarises the immune mechanisms involved in the pathogenesis of SLE and the site of action of various therapeutic targets.

Assessments of SLE disease activity

Trials involving SLE therapy have employed various instruments for assessment of disease activity. Traditional systems include the British Isles Lupus Assessment Group (BILAG) index and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [4]. The BILAG index is a scoring system in which activity in different organs/systems is scored separately while SLEDAI is a calculator of overall disease activity. SLE Responder Index (SRI) is a novel instrument for assessing improvements in disease activity without worsening the overall condition or the development of significant disease activity in new organ systems. It is defined as: first, a $\geq$4 point reduction in the SELENA-SLEDAI score; second, no new BILAG A, or no more than one new BILAG B domain score; third, no deterioration from baseline in the physician's global assessment by $\geq$0.3 points [5].

What is available now?

Belimumab is licensed for use in SLE in Europe and North America [6••,7••]. Rituximab (RTX) has been used

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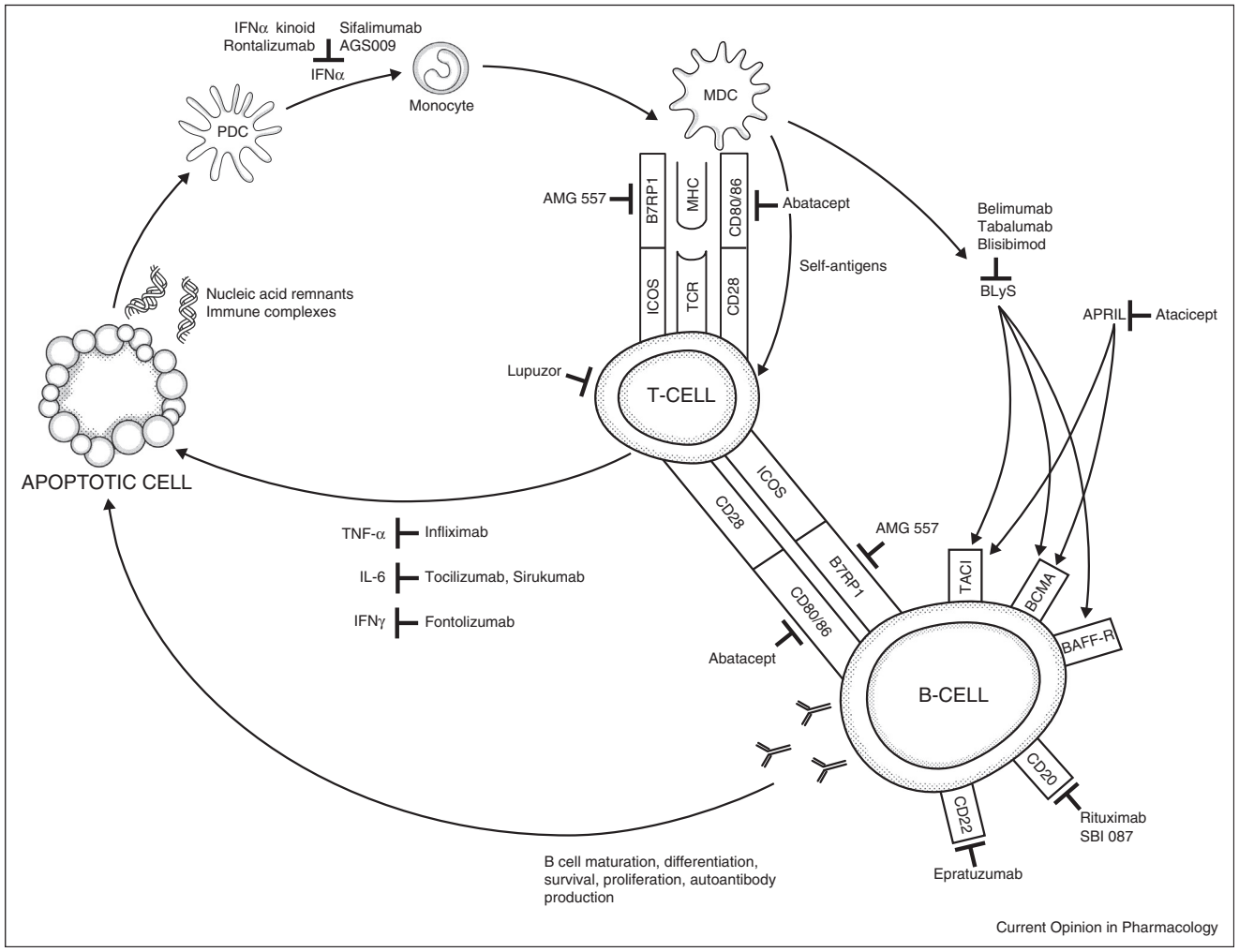
Figure 1



Pathogenesis of SLE and targets of biological therapy for SLE. pDC: plasmacytoid dendritic cell; mDC: myeloid dendritic cell; TACI: transmembrane activator and calcium modulator ligand interactor.
BCMA: B-cell maturing antigen; BAFFR: B-cell activating factor receptor; BLyS: B lymphocyte stimulator; APRIL: a proliferation-inducing ligand; ICOS: inducible co-stimulator; B7RP1: B7-related peptide 1; IFNα: interferon alpha; TCR: T-cell receptor; MHC: major histocompatibility complex. Cell death and deficient clearance of apoptotic debris leads to an abundance of nucleic acid remnants like DNA, RNA, which stimulate pDCs to produce IFNα, which, in turn, stimulates monocytes to differentiate into mature antigen presenting cells, mDCs. mDCs act to present self-antigens and other proteins (including BLyS and APRIL) to T and B cells, leading to cell proliferation, maturation, differentiation and survival, and excess autoantibody and cytokine production. Interaction of the T-cell receptor with major histocompatibility complex on antigen presenting cells triggers the T-cell response. However, T-cells need a second co-stimulatory signal to fully activate B cells. This co-stimulation is mediated by several pairs of co-stimulatory molecules, including CD28:B7 and CD40:CD40 ligand. All these processes eventually lead to further tissue damage and cell death, perpetuating the pro-inflammatory cycle. mAbs against CD20 and CD22 surface antigens lead to B-cell depletion, while anti-BLyS and anti-APRIL therapies affect B-cell survival. BLyS engages three receptors on the B-cell, that is, TACI, BCMA and BAFFR, while APRIL engages two, that is, TACI and BCMA. Abatacept and AMG557 interfere with T-cell co-stimulation, leading to suppression of T cell function, Lupuzor also inhibits T-cell function. Anti-IFN therapy prevents monocytes from maturing into mDCs and subsequently suppresses the pro-inflammatory activities of T-cells.

off-label successfully [8•] despite negative results in large randomised controlled trials (RCTs) in SLE. Although Abatacept is licensed for RA, it failed to meet primary end-points in SLE trials, but it has shown some promise in ameliorating lupus arthritis and nephritis [9•,10•].

Belimumab

Belimumab is a human IgG1λ monoclonal antibody (mAb) that binds soluble human BLys and inhibits its biological activities [6••,7••]. BLyS is overexpressed in SLE and correlates with changes in disease activity [11].

The two landmark phase III trials that led to the approval of belimumab were BLISS-52 [6••] and BLISS-76 [7••]. In both trials, intravenous (IV) belimumab 10 mg/kg plus standard of care (SOC) therapy met the primary endpoint of significantly higher SRI response rates at week 52 than with placebo plus SOC [6••,7••]. Patients with severe

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