

B-Cell-Directed Therapy for Inflammatory Skin Diseases

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The basic understanding of inflammatory dermatoses and autoimmune-mediated skin disorders has greatly advanced and broadened our understanding of underlying immune mechanisms that shape the complex network of chronic inflammation and autoimmunity. The new treatment options for psoriasis exemplify how new insights into (auto)immune responses, especially the role and function of various immune cells and proinflammatory cytokines, may lead to new therapeutic strategies. The concept of targeting B cells in autoimmune-mediated disorders is closely related to the discovery of autoantibodies and their cellular origin. However, the appreciation of B cells in autoimmunity has significantly changed and is not limited to their role as progenitors of autoantibody secreting plasma cells. Recent investigations of various inflammatory skin diseases, that is, autoimmune blistering disorders, collagen vascular diseases, and atopic dermatitis, actually support the concept that B cells might be as important as T cells in the etiopathogenesis of these disorders. The striking clinical improvement seen in patients with rheumatoid arthritis following B-cell depletion with the anti-CD20 mAb rituximab has tremendously catalyzed the interest in B-cell-targeted therapies in different autoimmune diseases. Future translational and clinical investigations are mandatory to precisely define the role and the contribution of impaired B-cell function in (auto)immune-mediated skin diseases.

Journal of Investigative Dermatology (2009) **129**, 289–301; doi:10.1038/jid.2008.192

INTRODUCTION

B cells play an important role in innate and adaptive immune processes. The aberrant regulation and activation of B cells result in a variety of chronic inflammatory and autoimmune-mediated disorders, respectively. In addition to their function as progenitors of (auto)-antibody-secreting plasma cells, B cells contribute to (auto)immune responses by various antibody (Ab)-independent mechanisms. They are capable of regulating T-cell activation and expansion by antigen presentation and expression of costimulatory signals (Mason, 1996). Moreover, several mouse models of different autoimmune diseases revealed the significant role of B cells in disease progression by release of cytokines and chemokines, respectively (Martin and Chan, 2004). Membrane-bound lymphotoxin α/β on the surface of B cells is effective in

activating the lymphotoxin β -receptor on stromal cells contributing to the formation of organized lymphoid tissues at sites of chronic inflammation, termed lymphoid neogenesis (Browning, 2006). In rheumatoid arthritis (RA) or primary Sjögren's syndrome (pSS), these ectopic lymphoid structures have been shown to develop a high degree of organization including distinct T- and B-cell zones, germinal center formation, and high endothelial venules, providing additional trafficking opportunities (Bombardieri *et al.*, 2007; Timmer *et al.*, 2007). The contribution of B cells to the complex pathogenesis of autoimmune diseases has become evident and better characterized by the recent application of B-cell-targeting therapeutic agents, especially the chimeric anti-CD20 Ab rituximab (Rituxan; Genentech Inc., Biogen Idec Inc.; and MabThera; Roche Inc.).

B CELLS IN DERMATOLOGICAL AUTOIMMUNE DISORDERS

Autoantibodies have been considered the hallmark of B-cell contribution to autoimmune diseases. There are a few autoimmune disorders in which the pathogenic relevance of the autoantibodies is well characterized; among those are autoimmune bullous disorders, particularly pemphigus and the pemphigoids. In most autoimmune diseases, such as systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and dermatomyositis, autoantibodies are not considered to play a direct role in disease pathogenesis, but provide clinically relevant diagnostic and prognostic criteria. Antinuclear antibodies serve as a sensitive diagnostic marker for SLE, but are also observed in a variety of other collagen vascular disorders, and their titers do not correlate with disease severity. It is

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Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B-cell-activating factor; BAFF-R, BAFF receptor; BCMA, B-cell maturation antigen; IVIG, intravenous immunoglobulin; PF, pemphigus foliaceus; PV, pemphigus vulgaris; pSS, primary Sjögren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TACI, transmembrane activator and calcium modulator and cyclophilin ligand interactor; TNF, tumor necrosis factor

Received 5 March 2008; revised 28 April 2008; accepted 10 May 2008

noteworthy that antinuclear antibodies are detectable in SLE patients before disease manifestation in the same way as circulating autoantibodies against desmoglein 1 (dsg1) are detectable in endemic forms of pemphigus foliaceus (PF) in Brazil (Fogo Selvagem) and Tunisia before disease onset (Kallel Sellami *et al.*, 2004; Hilario-Vargas *et al.*, 2006). These findings raise the question: to what extent do circulating autoantibodies contribute directly to disease manifestation or point to the presence of autoreactive B cells? However, additional triggering events, that is, infections and inflammation, may drive the initially nonpathogenic immune response to autoaggressive chronic immune events. A recent study in a mouse model of pemphigus vulgaris (PV) suggests that a concerted effect of monoclonal dsg3-reactive IgG autoantibodies is required to induce blister formation, leading to the hypothesis that synergistic effects of various autoantibodies are necessary to induce disease manifestation (Kawasaki *et al.*, 2006). The pathogenicity of autoantibodies in autoimmune disorders is not restricted to direct binding to the target structure leading to its loss of function, but includes indirect effects such as complement activation or the formation and deposition of circulating immune complexes that cause severe organ damage, including glomerulonephritis and vasculitis. In this context, polymorphisms of the low- and high-affinity Fc receptors were described to be associated with distinct autoimmune disorders, such as SLE or immune-mediated thrombocytopenia (Binstadt *et al.*, 2003). B cells undergo a complex development from hematopoietic precursors to mature short- and long-lived plasma cells. Wardemann *et al.* (2003) demonstrated that 50–70% of human B-cell precursors exhibit autoreactive antibodies, although the mature B-cell compartment contains only few self-reactive B cells. Self-reactive (autoreactive) B cells are deleted at certain stages of B cell development. The study by Wardemann *et al.* (2003) suggests that the depletion of these autoreactive B cells occurs at the stage of immature B cells and at the transition of new emigrant (i.e. leaving

the bone marrow) and mature B cells in the periphery. A recent study by Yurasov *et al.* (2005) revealed that in SLE patients 25–50% of the naïve mature B-cell population produce autoantibodies, indicating that defective regulatory mechanisms at early stages of B-cell development account for loss of self-tolerance. The successful use of B-cell-depleting therapies in (auto)immune-mediated skin disorders that are not considered primarily B cell dependent, such as atopic dermatitis, points to the important function of B cells beyond the secretion of (auto)antibodies. Although autoantibodies have not been identified in psoriasis and psoriasis arthritis, recent investigations showed ectopic lymphoid neogenesis in synovial tissues of psoriasis arthritis patients, suggesting an effective role of B cells and probably their secreted signaling molecules in disease progression (Canete *et al.*, 2007). In SSc, there is recent evidence that early-activated B cells interact with both endothelial cells and fibroblasts through the release of (auto)antibodies and cytokines such as IL-6, promoting fibrosis (Sakkas *et al.*, 2006). The release of various pro- and anti-inflammatory cytokines by B cells is considered to contribute to the inflammatory (auto)immune response in several dermatological disorders, for example, psoriasis, atopic dermatitis, and SSc, although the precise function of B cells in the pathogenesis of these diseases is not yet completely understood. These findings suggest that B-cell-directed therapy might provide an important therapeutic opportunity for a variety of dermatological diseases.

STRATEGIES OF B-CELL-DIRECTED THERAPY

Different approaches to targeting B-cell function are currently introduced, including the development of (i) antibodies that are directed against surface markers, which are preferentially expressed by B cells (that is, CD20, CD22) and (ii) inhibitors of survival and signaling factors that are crucial for B-cell activation (B-cell-activating factor (BAFF)/ a proliferation-inducing ligand (APRIL)) and T cell-B cell interaction (CD40/CD40L).

Antibodies against cell-surface markers
Anti-CD20 Ab (rituximab). Among the various mAbs used for targeting B cells, the chimeric IgG₁ anti-CD20 Ab, rituximab, has gained major clinical application. CD20 is a four transmembrane phosphoprotein that is expressed on most B cells from the late pre-B-cell stage until terminal plasma cell differentiation (Cragg *et al.*, 2005). Originally, the lack of CD20 expression in autoantibody-secreting plasma cells questioned the usefulness of employing rituximab in autoimmune diseases. Moreover, the physiological function of the CD20 receptor remains obscure, partly due to its still unknown ligand.

The successful treatment of B-cell lymphomas catalyzed the application of the anti-CD20 mAb rituximab in various, mostly autoantibody-mediated, autoimmune disorders. In 2007, rituximab was approved by the FDA for the treatment of RA patients who demonstrated an inadequate response to antitumor necrosis factor (TNF)-therapy. Rituximab induces B-cell lysis mainly by Ab-dependent cell-mediated cytotoxicity, but complement-dependent cytotoxicity and direct proapoptotic signals are discussed as well, although recent studies in mouse models demonstrated a predominant role for Fc-receptor-mediated effects of anti-CD20 treatment (Uchida *et al.*, 2004).

Depending on the compartment and the microenvironment, the sensitivity to anti-CD20 treatment and the kinetics of B-cell depletion show significant variations. In human CD20 BAC (bacterial artificial chromosome)-transgenic mice, peritoneal B1 cells and germinal center B cells demonstrate relative resistance to anti-CD20 administration, whereas circulating B cells are rapidly depleted (Gong *et al.*, 2005; Hamaguchi *et al.*, 2005). Moreover, marginal zone B cells are less affected by anti-CD20 depletion compared with follicular B cells in the spleen. Vugmeyster *et al.* (2005) demonstrated in cynomolgus monkeys that the depletion of splenic B cells was more profound compared with lymph node B cells after treatment with the fully humanized anti-CD20 Ab PRO70769. The contribution of the different B-cell populations to human autoimmune disorders is largely unknown. There-

fore, it is unclear whether the preferential depletion of peripheral blood-naïve B cells after rituximab therapy has any implication for its clinical use in autoimmune diseases. In humans, the effect of anti-CD20 Ab treatment on tissue B-cell populations has been investigated in RA and pSS (Pers *et al.*, 2007; Thurlings *et al.*, 2008; Vos *et al.*, 2007). One month after rituximab treatment, 3 out of 17 RA patients demonstrated a complete depletion of synovial B cells, 11 patients showed a partial depletion, and 3 patients did not show any synovial B cells before rituximab treatment (Vos *et al.*, 2007). The same group investigated the effect of rituximab on the inflammatory infiltrate in synovial tissue of 24 RA patients (Thurlings *et al.*, 2008). One month after rituximab, there was a significant decrease but not a complete depletion of synovial B cells in all patients, followed by a further reduction of B cells 16 weeks after treatment in some patients. At that time point, the authors noticed a pronounced decrease in synovial

macrophages, T cells, and plasma cells, which partially correlated with the clinical response (Thurlings *et al.*, 2008). These early observations suggest an important role for B cells in sustaining the autoimmune response at the primary site of inflammation in RA. A confirmatory study in pSS demonstrated that in eight patients, rituximab treatment induced a complete B-cell depletion in salivary glands that lasted for up to 24 months after treatment (Pers *et al.*, 2007). As shown for RA and SLE, in pemphigus, a rapid and complete depletion of CD19⁺ circulating B cells was noticed within days after the first infusion of rituximab. On average, depletion of peripheral CD19⁺ B cells lasted for 6–9 months but persisted up to 15 months in some PV patients (Eming *et al.*, 2008).

Effect of rituximab on non-B-cell populations in autoimmunity. There is increasing evidence that in addition to direct B-cell depletion, rituximab treatment exerts effects on distinct immune cells like autoreactive T effector cells

(Eming *et al.*, 2008), regulatory T cells (Sfikakis *et al.*, 2007), and monocyte-derived macrophages (Toubi *et al.*, 2007) (Figure 1). Seven SLE patients with active nephritis were treated with rituximab ($4 \times 375 \text{ mg m}^{-2}$), and mRNA expression of genes associated with regulatory T cells was determined in peripheral blood mononuclear cells by real-time PCR (Sfikakis *et al.*, 2007). In all seven SLE patients, mRNA levels of the T-regulatory markers interleukin 2 receptor alpha subunit (IL-2R alpha) (CD25), cytotoxic T-lymphocyte antigen-4 (CTLA-4), glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR), forkhead box P3 (FOXP3), and transforming growth factor beta (TGF- β) increased significantly following B-cell depletion, whereas mRNA expression of the costimulatory molecule, CD40L, was profoundly reduced. The authors found that increased FOXP3 mRNA levels persisted in peripheral blood mononuclear cells of patients in clinical remission, whereas peripheral blood mononuclear cells from relapsing

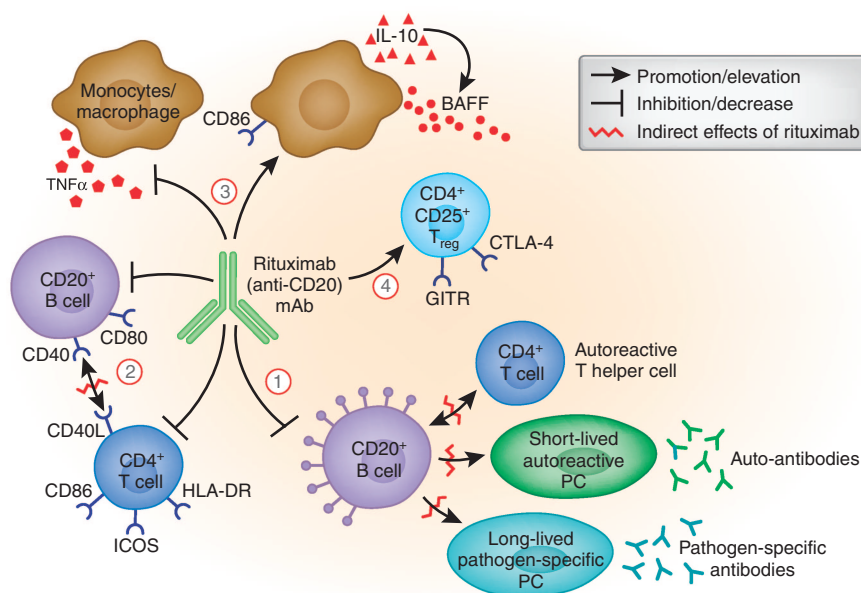


Figure 1. Effects of rituximab in autoantibody-mediated disorders. (a) The mAb rituximab induces the depletion of CD20⁺ B cells resulting in a decreased *de novo* generation of short- and long-lived plasma cells (PC). Secondly, rituximab interrupts the interaction between autoreactive T helper (Th) cells and antigen-presenting B cells. (b) Rituximab leads to significant reduction of CD40 and CD80 expression on B cells (Tokunaga *et al.*, 2005, 2007) as well as CD69, ICOS, HLA-DR, and CD40L expression on CD4⁺ Th cells (Tokunaga *et al.*, 2007; Sfikakis *et al.*, 2005a,b). Thus, important costimulatory signals, for example, through the CD40-CD40L pathway, regulating T-cell-B-cell interactions, are interrupted, preventing the action of autoreactive immune processes (Desai-Mehta *et al.*, 1996). (c) Rituximab inhibits the release of proinflammatory cytokines such as TNF- α by monocyte-derived macrophages, whereas the secretion of BAFF and IL-10 is increased. Moreover, IL-10 stimulates the secretion of BAFF in an autocrine/paracrine manner. CD86 surface expression on monocytes/macrophages (M ϕ) is enhanced (Toubi *et al.*, 2007). (d) Rituximab directly induces CD4⁺CD25⁺ regulatory T cells (T_{Reg}) identified by increased mRNA expression of Foxp3, GITR, and CTLA-4 (Vigna-Perez *et al.*, 2006; Sfikakis *et al.*, 2007; Vallerskog *et al.*, 2007).

patients demonstrated decreasing FOXP3 levels (Sfikakis *et al.*, 2007). A study by Vallerskog *et al.* (2007) demonstrated an increase of both activated CD4⁺CD25⁺ T cells and CD4⁺CD25^{bright}FOXP3⁺ regulatory T cells in 11 SLE patients after rituximab therapy. The results of these studies suggest that modulation of regulatory T-cell function might contribute to the clinical effect of rituximab treatment in SLE. In addition to these findings in SLE, a recent study by Stasi *et al.* (2008) suggests a restorative effect of transient B-cell depletion on abnormal regulatory T-cell function in idiopathic thrombocytopenic purpura. In this study, CD4⁺FOXP3⁺ regulatory T cells from peripheral blood of 26 idiopathic thrombocytopenic purpura patients receiving rituximab therapy were investigated by flow cytometry and their suppressive capacity was analyzed *in vitro* before and 3 months after rituximab therapy (Stasi *et al.*, 2008). In idiopathic thrombocytopenic purpura patients who responded to anti-CD20 Ab treatment, the authors noticed restored numbers and a restored regulatory function of CD4⁺FOXP3⁺ T cells compared with pretreatment data.

The most obvious reason for applying anti-CD20 Ab treatment in pemphigus is the removal of precursors of autoantibody-secreting plasma cells. Several lines of evidence point to the important role of autoreactive CD4⁺ T cells in the initiation and perpetuation of autoantibody secretion in pemphigus (Wucherpfennig *et al.*, 1995; Lin *et al.*, 1997; Tsunoda *et al.*, 2002; Hertl *et al.*, 2006). In this context, the depletion of autoreactive B cells as antigen-presenting cells might exert an indirect effect on dsG3-specific CD4⁺ T cells. A recent study by our group demonstrates a statistically significant decrease of dsG3-reactive CD4⁺ T cells in PV patients on rituximab treatment (Eming *et al.*, 2008). In a cohort of 11 PV patients treated with rituximab ($4 \times 375 \text{ mg m}^{-2}$), the frequencies of dsG3-reactive, peripheral Th1 (interferon- γ ⁺) and Th2 (IL-4⁺) cells were determined over a period of 12 months after rituximab treatment. Whereas frequencies of total CD3⁺CD4⁺ T helper cells remained unaffected by rituximab, the frequencies of autoreactive Th1 and Th2 cells

decreased significantly for 6 and 12 months after therapy, respectively. Interestingly, the frequencies of interferon- γ ⁺ tetanus toxoid-reactive T cells were not affected, suggesting that dsG3-specific CD4⁺ T cells strongly depend on autoreactive B cells as antigen-presenting cells (Eming *et al.*, 2008). This finding is strengthened by a recent mouse study providing evidence that B cells contribute to T-cell activation and expansion (Bouaziz *et al.*, 2007). This report clearly demonstrated that anti-CD20-mediated B-cell depletion significantly reduced CD4⁺ T-cell responses to self-antigens in models of collagen-induced arthritis, autoimmune diabetes (non-obese diabetic (NOD) mice), and to pathogens such as *Listeria monocytogenes* (Bouaziz *et al.*, 2007).

Impact of B-cell-depleting therapies on B-cell function in autoimmune disorders.

To date, rituximab has been investigated in a plethora of autoimmune disorders, including RA, SLE, idiopathic thrombocytopenic purpura, vasculitides, and several dermatological disorders (Table 1). Most of the information on B-cell function altered by anti-CD20 Ab treatment in autoimmune diseases results from clinical trials performed predominantly in RA and from smaller studies in patients with SLE and pSS. Although rituximab induces a profound depletion of circulating B cells, several studies demonstrated that rituximab does not significantly reduce serum levels of total IgM, IgG, or IgA in RA, SLE, or Wegener's granulomatosis (Cambridge *et al.*, 2003; Vallerskog *et al.*, 2007; Ferraro *et al.*, 2008). Moreover, there is no statistically significant decline in autoantibodies to common pathogens (cytomegalovirus, Epstein-Barr virus) or recall antigens such as tetanus toxoid after anti-CD20 Ab treatment (Cambridge *et al.*, 2003; Ferraro *et al.*, 2008). A recent study by Nagel *et al.* (Nagel A, Podstawa E, Eickmann M, Hertl M, Eming R, Rituximab mediates a strong elevation of B cell activating factor (BAFF) associated with increased pathogen-specific IgG but not antibodies in pemphigus vulgaris, submitted) showed an increase in anti-varicella-zoster-virus-IgG and anti-Epstein-Barr virus-IgG titers in 11 PV

patients on rituximab. Various studies focused on the relationship between reconstitution of circulating B-cell subsets and disease relapse after rituximab therapy (Leandro *et al.*, 2006; Roll *et al.*, 2006), indicating that B-cell recovery is associated with an increased number of B cells expressing a transitional phenotype (IgD⁺, IgM⁺, CD10⁺, CD24⁺, CD38^{high}, and CD27⁻) and with increasing numbers of B cells demonstrating a plasmablast phenotype (CD27^{high}, CD38^{high}, CD20⁻, IgD⁻). In RA, Leandro *et al.* (2006) demonstrated that disease relapse was associated with a higher frequency of memory B cells at the time of B-cell repopulation. A very interesting aspect of B-cell-directed therapy in autoimmune disorders is the correlation of autoantibody levels and disease response. In systemic autoimmune disorders, such as RA and SLE, the relationship between B-cell depletion, alterations in autoantibody titers, and clinical response is inconsistent (Cambridge *et al.*, 2006; Cohen *et al.*, 2006). On the other hand, in organ-specific autoimmunity (i.e., PV and PF), the rituximab-induced decline in circulating IgG autoantibodies mostly correlates well with clinical remission (Ahmed *et al.*, 2006; Joly *et al.*, 2007; Eming *et al.*, 2008). Apparently, autoreactive B cells in RA and SLE are of pathogenic relevance besides the production of autoantibodies probably through their function as antigen-presenting and cytokine-releasing cells, and B-cell depletion might exert its clinical effect through these mechanisms.

Following this line of thought, a recent study by Simon *et al.* (2008) revealed the potential role of B cells in the pathogenesis of atopic eczema. In this study, six patients with atopic dermatitis treated with rituximab ($2 \times 1,000 \text{ mg}$) demonstrated a significant reduction of the eczema area and severity index within 8 weeks following anti-CD20 Ab treatment (Simon *et al.*, 2008). Moreover, the authors noticed a reduction of CD20⁺ B cell infiltrates as well as decreased mRNA levels of IL-5 and IL-13 in lesional skin biopsies. These preliminary findings suggest that B cells play a crucial role as antigen-presenting cells and activators of T cells in the pathogenesis of atopic dermatitis.

Table 1. Rituximab in dermatological diseases: treatment schedules and clinical results

Rituximab regimen intravenous dose (mg m ⁻² body surface area) ¹	Clinical response	Selected references
Primary cutaneous B-cell lymphoma		
Single infusion: 375 Weekly: 4 × 375, 6 × 375, 8 × 375 Intralesional therapy: 10–30 mg ¹ rituximab per lesion three times weekly repeated every 28 days for 6 months or weekly for 5 consecutive weeks → without concomitant IS	Partial or mostly complete remission with resolution of skin lesions Intralesional therapy: tumor regression even of lesions that have not been injected Intralesional therapy is characterized by application of smaller doses of rituximab, but increased recurrence rate compared with intravenous therapy	(Heinzerling <i>et al.</i> , 2000a,b; Paul <i>et al.</i> , 2001; Bonnekoh <i>et al.</i> , 2002; Fink-Puches <i>et al.</i> , 2005; Lacouture <i>et al.</i> , 2005; Roguedas <i>et al.</i> , 2005; Kerl <i>et al.</i> , 2006; Nagasaki <i>et al.</i> , 2006)
Bullous skin diseases: pemphigus vulgaris including childhood/juvenile pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, bullous pemphigoid, mucous membrane pemphigoid, and epidermolysis bullosa acquisita		
Weekly: 2 × 375, 4 × 375 4 × 375 weekly followed by 1 × 375 monthly and later 3-month intervals 4 × 375 weekly followed by 2 × 375 biweekly Two cycles 3 × 375 weekly followed by 1 × 2 g/kg body weight IVIg in the fourth week → with concomitant IS	Partial or complete remission according to strong improvement of main clinical signs (cutaneous and mucocutaneous lesions), autoantibody titers, and reduction of concomitant IS	(Salopek <i>et al.</i> , 2002; Cooper <i>et al.</i> , 2003; Goebeler <i>et al.</i> , 2003; Dupuy <i>et al.</i> , 2004; Espana <i>et al.</i> , 2004; Arin <i>et al.</i> , 2005; Kong <i>et al.</i> , 2005; Schmidt <i>et al.</i> , 2005, 2006, 2007; Ahmed <i>et al.</i> , 2006; Niedermeier <i>et al.</i> , 2006, 2007; Carr and Heffernan, 2007; Crichlow <i>et al.</i> , 2007; Joly <i>et al.</i> , 2007)
Systemic lupus erythematosus (SLE) including lupus nephritis, neuropsychiatric, and childhood-onset SLE		
Single infusion: 100, 375, 1,000 ¹ Weekly: 2 × 375, 4 × 375, 4 × 500 Biweekly: 2 × 500, 2 × 750, 2 × 1,000 ¹ Rarely other doses → with or without concomitant IS	Partial or complete remission according to BILAG-, SLAM-, and SLEDAI-scores Fast improvement of skin and mucocutaneous lesions Improvement of lupus nephritis according to decline in proteinuria	(Anolik <i>et al.</i> , 2004; Looney <i>et al.</i> , 2004; Marks <i>et al.</i> , 2005; Sfrikakis <i>et al.</i> , 2005a,b; Tokunaga <i>et al.</i> , 2005, 2007; Smith <i>et al.</i> , 2006; Willems <i>et al.</i> , 2006; Jonsdottir <i>et al.</i> , 2008; Ng <i>et al.</i> , 2007; Tanaka <i>et al.</i> , 2007; Walsh and Jayne, 2007)
Primary Sjögren's syndrome including anterior scleritis		
Weekly: 2 × 375, 4 × 375 → without concomitant IS	Partial or complete remission according to subjective parameters like fatigue and dryness or VAS score Objective parameters like ophthalmological evaluation or Ab titers were not changed	(Ahmadi-Simab <i>et al.</i> , 2005; Pijpe <i>et al.</i> , 2005; Devauchelle-Pensec <i>et al.</i> , 2007)
Dermatomyositis including juvenile dermatomyositis		
Weekly: 4 × 100, 4 × 375 Biweekly: 2 × 1,000 ¹ → with or without concomitant IS	Partial remission according to reduction of DSSI and muscle strength deficit significant improvement of skin lesions Objective parameters like ophthalmologic evaluation or Ab titers were not changed	(Levine, 2005; Chung <i>et al.</i> , 2007; Cooper <i>et al.</i> , 2007; Dinh <i>et al.</i> , 2007)
Antineutrophil cytoplasmic Ab (ANCA)-associated vasculitis including Churg–Strauss syndrome, microscopic polyangiitis, mixed cryoglobulinemia, and Wegener's granulomatosis		
Weekly: 2 × 250, 3 × 375, 4 × 375, 4 × 500 ¹ Biweekly: 2 × 500 ¹ , 2 × 1,000 ¹ 4-weekly: 4 × 275 → with or without concomitant IS	Partial or complete remission according to strong improvement of main clinical signs (or BVAS Score) In some cases, stability of disease manifestation or rather progression (mainly retro-orbital granulomas) Decline or stability of ANCA titers Strong improvement of cutaneous manifestations	(Zaja <i>et al.</i> , 2003; Eriksson, 2005; Ferraro <i>et al.</i> , 2005; Kallenbach <i>et al.</i> , 2005; Keogh <i>et al.</i> , 2005; Aries <i>et al.</i> , 2006; Kaushik <i>et al.</i> , 2006; Keogh <i>et al.</i> , 2006; Koukoulaki <i>et al.</i> , 2006; Smith <i>et al.</i> , 2006; Visentini <i>et al.</i> , 2007; Walsh and Jayne, 2007)
Atopic eczema		
Biweekly: 2 × 1,000 ¹ → with concomitant IS	Significant improvement of AE lesions according to reduction of EASI and pruritus score	(Simon <i>et al.</i> , 2008)
BILAG, British islet lupus assessment group; BVAS, Birmingham vasculitis activity score; DSSI, dermatomyositis skin severity index; EASI, eczema area and severity index; IS, immunosuppressive treatment; IVIg, intravenous immunoglobulin; SLAM, systemic lupus activity measure index score; SLEDAI, SLE disease activity index; VAS, visual analog scales. ¹ Denotes mg total dose.		

Anti-CD20 Ab therapy in blistering skin disorders. The first reports of rituximab treatment in patients with autoimmune bullous diseases de-

scribed two female patients with paraneoplastic pemphigus (Borradori *et al.*, 2001; Heizmann *et al.*, 2001). Heizmann *et al.* reported a complete

remission of conjunctival and mucocutaneous lesions within 6 months after rituximab therapy and Borradori *et al.* described the rapid improvement of

mucosal erosions 3 months after anti-CD20 treatment. Up to now, one additional case report demonstrated a good clinical response of otherwise resistant paraneoplastic pemphigus, although there are three published cases describing a lack of efficacy of anti-CD20 therapy in paraneoplastic pemphigus due to the poor prognosis of the underlying malignancies (Hoque *et al.*, 2007).

In autoimmune bullous diseases, rituximab has been used mostly to treat PV and PF. The clinical efficacy of rituximab treatment is shown in a representative PV patient (Figure 2), and it has been described by several cohort studies and most recently a multicenter study using a single cycle of rituximab in 14 PV and seven PF patients with otherwise recalcitrant disease (Joly *et al.*, 2007). In this study, anti-CD20 therapy (rituximab $4 \times 375 \text{ mg m}^{-2}$) was applied in an adjuvant setting based on systemic glucocorticoids and adjuvant immunosuppressives. Eighteen of 21 patients experienced complete remission within 3 months after rituximab therapy, and nine patients relapsed after a mean of 19

months (Joly *et al.*, 2007). A recent study by Ahmed *et al.* (2006) combined rituximab with high-dose intravenous immunoglobulin (IVIG) treatment in 11 PV patients with inadequate responses to conventional immunosuppression and IVIG alone. During the first 2 months, these patients received three weekly infusions of rituximab (375 mg m^{-2}) followed by IVIG (2 g kg^{-1}) in the fourth week, whereas in months 3–6, rituximab was administered once per month plus a single infusion of 2 g kg^{-1} of IVIG. Nine of 11 patients experienced a complete remission within 7–9 weeks after the first rituximab infusion, lasting between 22 and 37 months, whereas 2 patients showed a relapse 12 months after beginning the study (Ahmed *et al.*, 2006). In this study, systemic immunosuppression was tapered after the first rituximab infusion and discontinued by the end of week 8.

Summarizing the numerous case reports and smaller cohort studies, more than 50 pemphigus patients have been treated with rituximab, mostly combined with systemic immunosuppressants. In most studies, rituximab

treatment led to a decrease of dsG1-/dsG3-reactive autoantibodies correlating well with clinical remission, although there are reports indicating a clinical response with persisting autoantibody levels (Herrmann *et al.*, 2003; Morrison, 2004). For the treatment of low-grade or follicular CD20⁺ B-cell lymphoma, the recommended dosing consists of 375 mg m^{-2} body surface area i.v. once weekly for four weeks. Originally, in most studies, this oncological treatment regimen has been adopted for the treatment of autoimmune diseases (Table 1). In blistering skin disorders, rituximab is generally applied in an adjuvant setting combined with systemic immunosuppressives, including corticosteroids, azathioprine, or mycophenolate mofetil (Hertl *et al.*, 2008). Different dosing regimens of rituximab have successfully been applied, as demonstrated in RA by the DANCER study, showing that two infusions with 500 and 1,000 mg rituximab on days 1 and 15 were highly effective in the treatment of active RA (Emery *et al.*, 2006). In the treatment of patients with autoimmune blistering skin disorders, the safety profile of rituximab is comparable with the results of previous studies in RA (Edwards *et al.*, 2004). Aside from infusion-related adverse events including headache, fever, chills, urticaria, and hypotension, a number of serious and fatal opportunistic bacterial and viral infections have been reported, especially in patients receiving high-dose immunosuppressive medication (Hertl *et al.*, 2008). Recently, a safety warning was announced by the FDA regarding the development of progressive multifocal leukoencephalopathy occurring in two SLE patients treated with rituximab (Berger, 2007).

Anti-CD22 Ab (epratuzumab). Besides the successful use of anti-CD20 treatment, other B-cell-specific surface markers such as CD19 and CD22 have recently become potential targets of Ab therapy (Table 2).

CD22 represents a 135 kDa lectin-like type I transmembrane glycoprotein belonging to the Ig superfamily, which is expressed at low levels on immature B cells and at higher levels on circulating mature IgD⁺ IgM⁺ B cells, whereas

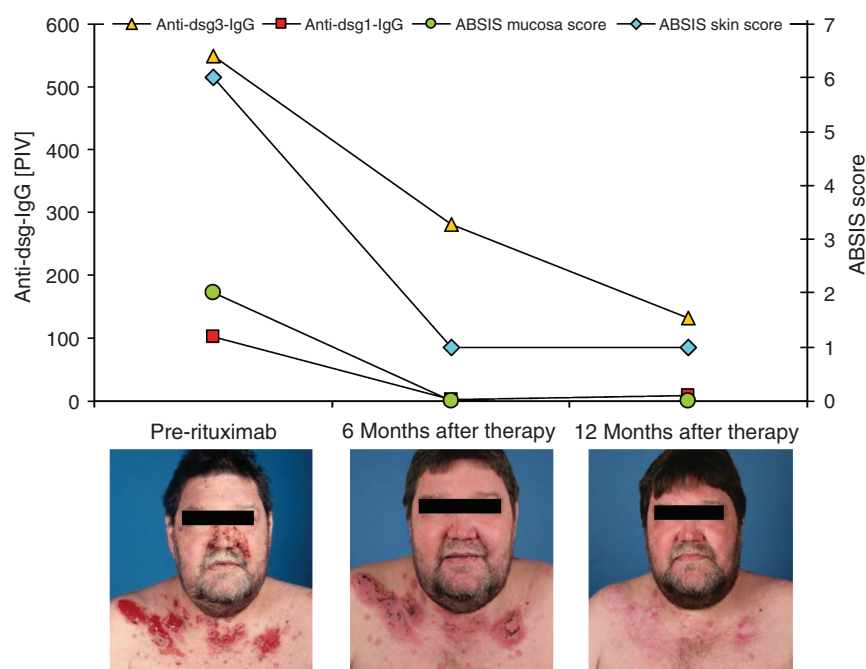


Figure 2. Clinical response to rituximab in pemphigus. The clinical course of a PV patient with severe erosions of skin and oral mucosa, resistant to long-term conventional immunosuppressive medication including high-dose prednisolone and mycophenolate mofetil is shown. Rituximab treatment led to a significant clinical remission reflected by a decline of the clinical score (autoimmune bullous skin disease intensity score [ABSIS]), which correlates with a decrease of anti-desmoglein (dsG)-3 and dsG-1 IgG titers for the entire observation period of 12 months.

differentiated plasma cells lack CD22 expression (Tedder *et al.*, 2005). Its function is not completely understood, but in addition to attenuating B-cell receptor signaling by cytoplasmic inhibitory motifs, it acts as a homing receptor for recirculating B cells (O'Keefe *et al.*, 1999). Consisting of 7 immunoglobulin-like domains, CD22 mediates adhesion to oligosaccharides bearing α 2,6-linked sialic acid residues that are present on most leukocytes and other serum components (Engel *et al.*, 1995).

Epratuzumab (hLL2), a humanized, monoclonal IgG₁ anti-CD22 Ab, binds to the third cytoplasmic Ig domain, inducing a rapid CD22 internalization and phosphorylation (Carnahan *et al.*,

2003). In contrast to rituximab, epratuzumab is considered as an immunomodulatory agent probably engaging the negative signaling effects of CD22 (Tedder *et al.*, 2005). Both in non-Hodgkin lymphoma and SLE, anti-CD22 Ab treatment leads to a modest (that is, 30–54%) reduction of peripheral B cells (Carnahan *et al.*, 2007). Recently, clinical studies including open label phase II trials were conducted in SLE and pSS patients. Steinfeld *et al.* (2006) treated 16 pSS patients with four infusions of 360 mg m⁻² epratuzumab every other week with a 6-month follow-up period. A total of 53% of the patients demonstrated a clinically relevant response for at least

18 weeks with moderately decreased (that is, 39–54%) circulating B cells. Dorner *et al.* (2006) analyzed the therapeutic efficacy and safety of epratuzumab in 14 SLE patients, showing a modest decline in B cells and clinical activity score (BILAG score, British Isles Lupus Assessment Group).

Inhibitors of survival and signaling factors

The B-cell-activating factor and a proliferation-inducing ligand system.

In the context of autoimmune disorders, B-cell tolerance and homeostasis are of major interest. Thus, factors influencing B-cell maturation have been thoroughly characterized in various autoimmune

Table 2. Current therapeutic strategies interfering with B-cell function in autoimmune skin diseases

Effect	Target	Agent	Origin	Clinical evidence level	References
B-cell depletion	CD20	Rituximab	Chimeric human/mouse IgG1 mAb	Clinical trials	(Browning, 2006; Stohl and Looney, 2006; Dorner and Lipsky, 2007; Arkfeld, 2008)
		Ha20 (IMMU-106)	Fully humanized mAb	Case report in SLE	(Tahir <i>et al.</i> , 2005; Fanale and Younes, 2007)
	CD22	Epratuzumab	Humanized IgG1 mAb	Clinical trials (SLE, pSS)	(Browning, 2006; Steinfeld <i>et al.</i> , 2006; Stohl and Looney, 2006; Carnahan <i>et al.</i> , 2007; Jacobi <i>et al.</i> , 2008)
Blocking survival signals/growth factor inhibition	BAFF	Belimumab (Lymphostat-B)	Fully human IgG1 mAb	Clinical trials (SLE)	(Baker <i>et al.</i> , 2003; Browning, 2006; Halpern <i>et al.</i> , 2006; Stohl and Looney, 2006; Chatham <i>et al.</i> , 2008; Wallace <i>et al.</i> , 2008)
		AMG 623	“Peptidbody”—fusion between Fc portion of IgG and a peptid-specific sequence of BAFF	Clinical trials (SLE)	(Stohl and Looney, 2006; Dorner and Lipsky, 2007)
	BAFF/APRIL	IVIg (anti-BAFF and anti-APRIL)	Polyclonal IgG selected from healthy donors	Clinical trials (DH, ABD)	(Le Pottier <i>et al.</i> , 2007)
		Atacicept (Taci-Ig)	Recombinant human fusion protein	Clinical trials (SLE)	(Stohl and Looney, 2006; Dall'era <i>et al.</i> , 2007; Dorner and Lipsky, 2007; Munafo <i>et al.</i> , 2007)
	CD22	Epratuzumab	Humanized IgG1 mAb	Clinical trials (SLE, pSS)	(Browning, 2006; Steinfeld <i>et al.</i> , 2006; Stohl and Looney, 2006; Carnahan <i>et al.</i> , 2007; Jacobi <i>et al.</i> , 2008)
Interference with proapoptotic signals	Fas, caspases	IVIg (anti-Fas)	Polyclonal IgG, selected from healthy donors	Clinical trials (DH, ABD)	(Prasad <i>et al.</i> , 1998)
Blocking immune complex signalling	FcR, FcRn	IVIg	Polyclonal IgG, selected from healthy donors	Clinical trials (DH, ABD)	(Li <i>et al.</i> , 2005; Browning, 2006)
Removal of serum IgG	IgG	Immunoadsorption (IA)	Protein A-based adsorption of IgG (including pathogenic IgG) and circulating immune complexes from plasma	Clinical trials (ABD)	(Eming and Hertl, 2006a, b; Shimanovich <i>et al.</i> , 2006, 2008; Niedermeier <i>et al.</i> , 2007)

ABD, autoimmune bullous diseases; APRIL, a proliferation-inducing ligand; BAFF, B-cell-activating factor; DH, dermatomyositis; IVIg, intravenous immunoglobulin; mAb, monoclonal antibody; pSS, primary Sjögren's syndrome; SLE, systemic lupus erythematosus.

diseases (Tangye *et al.*, 2006). The B-cell activation factor from the tumor necrosis family (BAFF, also known as BLyS (B lymphocyte stimulator)) represents a key survival factor for B-cell development, whose complex function for B-cell tolerance is not completely defined yet (Mackay *et al.*, 2003; Schneider, 2005). There are three different BAFF receptors: B-cell maturation antigen (BCMA); transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI); and BAFF receptor (BAFF-R), of which BCMA and TACI are shared with another ligand of the TNF family, a proliferation-inducing ligand (APRIL). Both BAFF and APRIL are expressed mainly by monocytes, macrophages, and dendritic cells, to a lesser extent by T cells, and also by nonlymphoid cells such as epithelial cells, stromal bone marrow cells, and synoviocytes (Mackay *et al.*, 2007). Depending on the state of maturation, B cells express BAFF-R, BCMA, and TACI in different intensities, whereas BAFF-R is also expressed by activated and regulatory T cells. BCMA has been identified on plasma cells and plasma blasts (Mackay *et al.*, 2007). Chang *et al.* (2006) found TACI expression on activated human macrophages, suggesting a role for BAFF in innate immunity. The complex physiological network of the BAFF/APRIL system goes

beyond the scope of this review and is extensively discussed elsewhere. In the following paragraphs, we will particularly focus on the recent understanding of the role of BAFF and APRIL in B-cell-mediated autoimmunity.

BAFF/APRIL in autoimmune disease.

Numerous studies in SLE, RA, and pSS consistently found increased levels of BAFF (Figure 3), APRIL, and even BAFF/APRIL heterotrimers in serum and target tissues, strengthening the pathogenic relevance of raised BAFF and APRIL, respectively (Pers *et al.*, 2005; Seyler *et al.*, 2005). Moreover, in pSS, SLE, and RA, elevated BAFF and/or APRIL serum levels correlate with autoantibody titers and/or disease activity in some patients (Cheema *et al.*, 2001; Zhang *et al.*, 2001; Jonsson *et al.*, 2005; Schaller *et al.*, 2005). Asashima *et al.* (2006) recently reported increased BAFF serum levels in patients with bullous pemphigoid but not in patients with PV. In a recent study by Matsushita *et al.*, BAFF serum levels were investigated in patients with localized scleroderma, bullous pemphigoid and PF/PV (Matsushita *et al.*, 2007b). In this study, 32% (14/44) of patients with localized scleroderma showed increased BAFF serum levels compared with healthy controls. Moreover, the

authors found a correlation between BAFF serum levels and disease severity, as 53% of the patients with generalized scleroderma, 27% with morphea, and 13% with linear scleroderma exhibited elevated BAFF serum levels (Matsushita *et al.*, 2007b). BAFF serum levels of patients with bullous pemphigoid and PF/PV were not significantly increased compared with healthy controls. A previous study by the same group investigated serum BAFF levels, BAFF mRNA in skin samples, and the expression of BAFF-R on peripheral B cells in 83 patients with SSc (Matsushita *et al.*, 2006). Compared with healthy individuals, BAFF serum levels in SSc patients were elevated and correlated with the extent of the disease. Furthermore, BAFF-R expression on CD19⁺ peripheral B cells was increased in SSc, as was BAFF mRNA expression found in biopsies of lesional skin (Matsushita *et al.*, 2006).

BAFF has been shown to play an important role in maintaining B-cell tolerance, as autoreactive B-cell clones show an impaired ability to respond to limited levels of BAFF leading to their depletion (Brink, 2006). On the other hand, strongly elevated serum levels of BAFF might propagate autoreactive B-cell clones by rescuing them from deletion (Thien *et al.*, 2004).

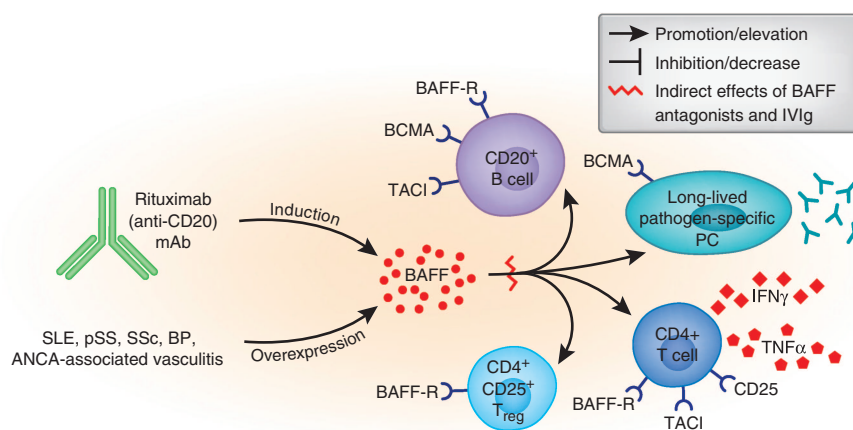


Figure 3. Rituximab exerts various immune functions by the induction of BAFF. BAFF is overexpressed in many autoimmune diseases like SLE, pSS, SSc, bullous pemphigoid (BP), and different antineutrophil cytoplasmic Ab (ANCA)-associated vasculitides. Furthermore, the generation and release of BAFF is increased after rituximab-induced B-cell depletion. By binding to its receptors BAFF-R, BCMA, and TACI, which are expressed on a variety of different lymphocyte subsets, BAFF exerts a central role in regulating immune responses. BAFF supports the *de novo* generation and survival of B lymphocytes and stimulates the survival of long-lived bone-marrow plasma cells (PC). Furthermore, BAFF increases the expression of CD25 on CD4⁺ Th cells as well as the release of TNF- α and interferon- γ by these cells (Huard *et al.*, 2001). Moreover, it has a promoting effect on the proliferation and survival of naturally occurring CD4⁺ CD25⁺ regulatory T cells (T_{reg}) (Ye *et al.*, 2004; Schneider, 2005). Therapeutic administration of BAFF antagonists or intravenous immunoglobulin (IVIg) interferes with these different effects of BAFF.

BAFF/APRIL in animal models of autoimmune diseases. The effect of elevated BAFF serum levels on self-reactive immune responses has been investigated using mouse models of various autoimmune diseases. BAFF-transgenic mice develop a phenotype resembling typical symptoms of human autoimmune disorders, including the presence of circulating immune complexes, immunoglobulin deposition in the kidneys, anti-DNA autoantibodies, and the presence of rheumatoid factors (Mackay *et al.*, 1999).

In a recent study, Matsushita *et al.* (2007a) investigated the role of BAFF in tight-skin mice, an animal model of SSc. The authors found elevated BAFF serum levels in these mice until 8 weeks of age compared with wild-type littermates, whereas no significant differences in expression of BAFF-R, BCMA, or TACI were noticed. Furthermore, neutralizing BAFF by treating tight-skin mice with BAFF-R-Ig reduced the development of skin fibrosis, decreased the production of anti-topoisomerase I antibodies, and attenuated the expression of IL-6 and IL-10, whereas it upregulated interferon- γ production in the skin of these animals (Matsushita *et al.*, 2007a).

Effect of rituximab treatment on BAFF and APRIL in autoimmune diseases. Numerous recent studies demonstrated increased serum BAFF levels upon peripheral B-cell depletion by rituximab treatment in RA, SLE, and pSS (Vallerskog *et al.*, 2006; Seror *et al.*, 2007).

A recent study by Nagel *et al.* (Nagel, A, Podstawa E, Eickmann M, Hertl M, Eming R, Rituximab mediates a strong elevation of B cell activating factor (BAFF) associated with increased pathogen-specific IgG but not anti-bodies in pemphigus vulgaris, submitted) investigated BAFF and APRIL serum levels in 11 PV patients following rituximab therapy, compared with PV patients treated with immunosuppression and immunoadsorption. Immunosuppressive therapy and adjuvant immunoadsorption altered neither BAFF nor APRIL serum levels, whereas rituximab induced a significant increase in BAFF levels as long as peripheral B-cell depletion persisted. Moreover, whereas anti-dsg1- and anti-

dsg3-IgG autoantibodies decreased, the titers of pathogen-specific IgG (anti-varicella-zoster-virus-IgG, anti-Epstein-Barr virus-IgG) were transiently increased 6 months after rituximab therapy, probably due to elevated BAFF levels enforcing Ab secretion by long-lived plasma cells. Of note, anti-CD20 Ab treatment did not affect APRIL serum levels, which remained unchanged in all 11 PV patients investigated (Nagel *et al.*, submitted; cited above).

Therapeutic manipulation of B-cell survival factors. The concept that impaired expression of BAFF and an imbalance of the BAFF/APRIL system enforce the development and maturation of autoreactive B-cell clones led to the development of new, BAFF-directed therapeutic approaches.

Animal models: A study by Ramanujam *et al.* (2006) investigated the effect of selective and nonselective BAFF blockade in a murine model of SLE (NZB/NZW F1 mice), demonstrating that both BAFF-R-Ig and TACI-Ig fusion proteins delayed the onset of SLE and improved mortality in this model. Both treatment regimens reduced the numbers of activated and memory T-cell subsets and induced comparable depletion of marginal zone and follicular B cells. In contrast to selective inhibition of BAFF by BAFF-R-Ig, blockade of BAFF and APRIL by TACI-Ig reduced serum IgM levels and, most strikingly, decreased the number of splenic plasma cells (Ramanujam *et al.*, 2006). Whether the absence of BAFF can prevent the *de novo* onset of an autoantibody-mediated disease has been addressed by developing BAFF-deficient New Zealand Mixed mice (Jacob *et al.*, 2006). In contrast to BAFF-competent New Zealand Mixed mice, BAFF-deficient animals demonstrated reduced germinal centers as well as lower numbers of Ig-secreting cells and T cells (Jacob *et al.*, 2006). Interestingly, at the age of 10–13 months, these mice showed serum Ig autoantibody levels (i.e., anti-histone-IgG and anti-ds-DNA-IgG) that reached wild-type levels, suggesting that autoreactive B cells are able to survive and produce autoantibodies in the absence of BAFF. Although BAFF-deficient

New Zealand Mixed mice were not protected from autoantibody production, renal pathology and clinical symptoms such as proteinuria were attenuated compared with BAFF-competent littermates, probably due to the skewed autoantibody profile in which IgG1 autoantibodies are the predominating isotype in BAFF-deficient animals (Jacob *et al.*, 2006).

Clinical trials: Belimumab (Lympho-Stat-B) is a fully human IgG $_{1\lambda}$ anti-BAFF mAb that targets soluble BAFF and has demonstrated modest efficacy in recent phase I/II studies in SLE and RA. Anti-BAFF therapy significantly reduces the number of activated CD69 $^{+}$ peripheral B cells in clinically responsive SLE patients, exhibiting few adverse effects (Stohl *et al.*, 2006). A total of 449 patients with active SLE were enrolled in a phase II, randomized, double-blind, placebo-controlled trial with belimumab (1, 4, and 10 mg kg $^{-1}$) in addition to standard immunosuppressive therapy for 52 weeks, followed by 1.5 years of open-label belimumab treatment. Belimumab treatment normalized hypergammaglobulinemia and reduced anti-dsDNA, anti-Sm and anti-RNP autoantibody levels compared with the placebo control group (Chatham *et al.*, 2008). Other approaches using BAFF receptor-Ig fusion protein (BR3-Ig) or a decoy receptor, TACI-Ig, are currently being explored. The possible impact of therapeutic administration of BAFF antagonists on immune cells is summarized in Figure 3.

FUTURE PERSPECTIVES

The various mechanisms by which B cells are involved in the induction and maintenance of autoimmune diseases are intensively investigated. In dermatology, the various functions of autoreactive B cells including T-cell activation via antigen presentation, secretion of proinflammatory cytokines, and production of self-reactive antibodies are increasingly appreciated in the treatment of autoimmune bullous disorders, SLE, dermatomyositis, SSc, and vasculitides. The use of the anti-CD20 Ab rituximab in severe pemphigus is its most familiar clinical application, while its use in

inflammatory disorders such as dermatomyositis, atopic dermatitis, chronic graft-versus-host disease and different vasculitides including anti-neutrophil cytoplasmic Ab-associated vasculitides awaits further analysis. In contrast to extensive use in SLE, cutaneous lupus erythematosus has not been treated with rituximab. Recent studies have evaluated fully humanized anti-CD20 mAbs that are expected to be less antigenic than rituximab (Genovese et al., 2006). Currently, the clinical effectiveness of targeting the B-cell survival factors BAFF and APRIL is being investigated in RA, SLE, and pSS. Furthermore, blockade of the CD40-CD40L interaction as well as neutralizing different cytokines such as IL-6, IL-21, and TNF- α , which are of importance for B-cell activation and differentiation, are being discussed as potential targets for innovative therapies in autoimmune disorders.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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