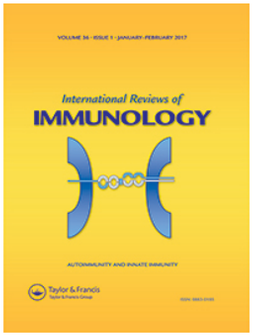

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Targeting BAFF and APRIL in systemic lupus erythematosus and other antibody-associated diseases

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ABSTRACT

The B cell-stimulating molecules, BAFF (B cell activating factor) and APRIL (a proliferation-inducing ligand), are critical factors in the maintenance of the B cell pool and humoral immunity. In addition, BAFF and APRIL are involved in the pathogenesis of a number of human autoimmune diseases, with elevated levels of these cytokines detected in the sera of patients with systemic lupus erythematosus (SLE), IgA nephropathy, Sjögren's syndrome, and rheumatoid arthritis. As such, both molecules are rational targets for new therapies in B cell-driven autoimmune diseases, and several inhibitors of BAFF or BAFF and APRIL together have been investigated in clinical trials. These include the BAFF/APRIL dual inhibitor, atacicept, and the BAFF inhibitor, belimumab, which is approved as an add-on therapy for patients with active SLE. *Post hoc* analyses of these trials indicate that baseline serum levels of BAFF and BAFF/APRIL correlate with treatment response to belimumab and atacicept, respectively, suggesting a role for the two molecules as predictive biomarkers. It will, however, be important to refine future testing to identify active forms of BAFF and APRIL in the circulation, as well as to distinguish between homotrimer and heteromer configurations.

In this review, we discuss the rationale for dual BAFF/APRIL inhibition versus single BAFF inhibition in autoimmune disease, by focusing on the similarities and differences between the physiological and pathogenic roles of the two molecules. A summary of the preclinical and clinical data currently available is also presented.

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APRIL; autoimmune disease; BAFF; SLE; TACI-Ig

Introduction

The B cell-stimulating molecules, BAFF (B cell activating factor) and APRIL (a proliferation-inducing ligand), are implicated in several human autoimmune diseases with autoreactive B cell involvement, including systemic lupus erythematosus (SLE) [1–10], IgA nephropathy (IgAN) [11–13], Sjögren's syndrome (SS) [14–16], and rheumatoid arthritis (RA) [17].

Members of the tumor necrosis factor (TNF) family, to which BAFF and APRIL belong [18–20], are trimeric molecules [19,21,22]. BAFF and APRIL bind to transmembrane activator and CAML interactor (TACI) and B cell maturation antigen (BCMA), while BAFF additionally binds to a third receptor, BAFF-R; all three receptors are expressed by B lineage cells [23–28]. APRIL, but not BAFF, can also bind heparan sulfate proteoglycans (HSPG) within the extracellular matrix or on the surface of cells such as plasma cells [29–32]. An overview of the protein configurations of BAFF and APRIL, as well as their receptors, can be seen in Figure 1.

BAFF maintains B cell homeostasis by acting as a survival and fitness factor for B cells from the transitional stage of development onwards, while APRIL appears to act at a later stage, modulating the function and survival of antigen-experienced B cells [23,33–36]. Both cytokines stimulate class-switch recombination (CSR), hence contribute to shaping humoral effector mechanisms. With regards to humoral memory, APRIL is involved in the establishment and survival of the long-lived plasma cell (LLPC) pool in the bone marrow (BM) [37–46], whereas the role of BAFF in this process is less clear [43]. Early reports from preclinical experiments in the NZB/W F1 mouse model of SLE comparing BAFF, APRIL or dual BAFF/APRIL blockade with BAFFR-Fc, an anti-APRIL antibody, or TACI-Fc, respectively, support the notion that BAFF and APRIL act in concert and at a flexible degree of interchangeability to support humoral memory via LLPC niche maintenance [47].

Elevated levels of BAFF and APRIL in the sera of patients with certain autoimmune diseases correlate

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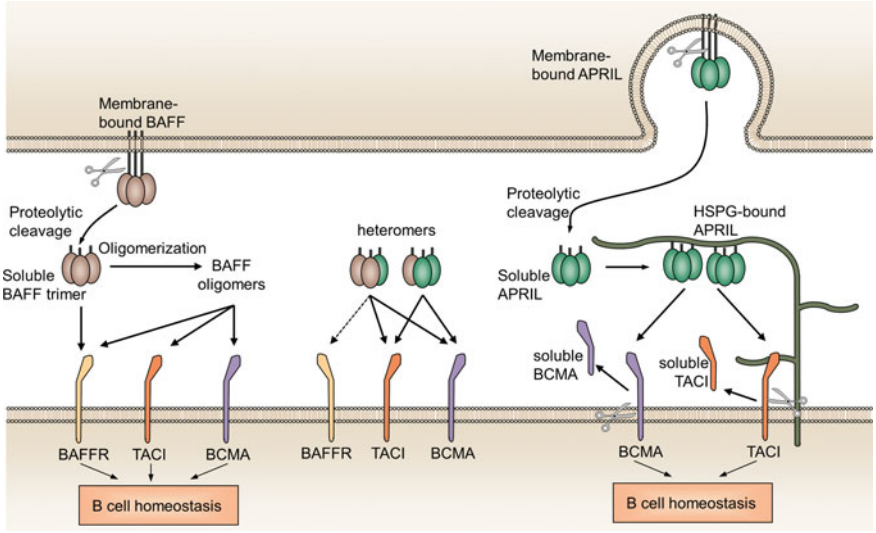

Figure 1. BAFF and APRIL receptor interactions. BAFF and APRIL are first synthetized as type II transmembrane proteins that are mainly expressed in cells of myeloid origin or stromal cells. They are processed to trimeric soluble cytokines by furin or furin-like protease(s). APRIL and BAFF can also assemble as heteromers containing two APRIL and one BAFF, or two BAFF and one APRIL protomers. The three receptors are type III transmembrane proteins (lacking signal peptides) mainly expressed by B cells at different stages of differentiation and whose main, but not exclusive function, is to provide survival and fitness signals to cells. BAFF-R binds BAFF only, and to a lesser extent BAFF-rich but not APRIL-rich heteromer. BAFF–BAFF-R interactions have a dominant role for the maintenance of the peripheral mature naïve B cell pool. TACI binds to both BAFF and APRIL but responds better, if not exclusively, to oligomeric ligands (i.e. containing more than one trimer: membrane-bound BAFF, BAFF 60-mer [containing 20 trimers] or heparan sulphate proteoglycan (HSPG)-bound APRIL). BCMA binds to APRIL with higher affinity than to BAFF. TACI can be cleaved by the ADAM10 metalloprotease to act as a soluble decoy receptor that inhibits both BAFF and APRIL. BCMA can be processed by γ-secretase, releasing a soluble decoy receptor that, in its monomeric form and because of its weak affinity for BAFF, inhibits APRIL only.

with disease severity [2,3,7,10–12,16,48–51] and levels of pathogenic autoantibodies [3-5,7,52,53], highlighting these molecules as therapeutic targets. Compounds targeting BAFF alone have been the subject of recent clinical investigations, and the BAFF inhibitor, belimumab, has been approved as add-on therapy for the treatment of patients with seropositive SLE [54,55]. Compounds inhibiting both BAFF and APRIL are being evaluated; in particular, atacicept, which is currently undergoing phase II clinical investigation for the treatment of patients with moderate-to-severe SLE (completion of primary analysis expected in 2016).

The aim of this review is to explore the potential advantages and drawbacks of targeting BAFF and APRIL together over BAFF alone by examining the biological properties and physiological roles of both molecules, as well as their respective roles in B cell-driven autoimmune diseases. Up-to-date data from preclinical and clinical studies of BAFF and APRIL antagonists will also be presented.

Biological properties of BAFF and APRIL

Characterization and configuration

BAFF, also known as BLyS (B Lymphocyte Stimulator), was first characterized by its capacity to co-stimulate B cell proliferation and induce immunoglobulin production *in vivo* [19,20]. It is a type II membrane protein that exists either in membrane-expressed or soluble cytokine forms, both of which are capable of eliciting B cell activation [19,20,56]. Soluble BAFF can be released as a trimeric molecule, which in neutral solution can combine to form 60-mers (20 trimers) via interaction of a unique extended loop [57,58]. APRIL was originally identified in the context of tumor cell growth and defined by its capacity to induce the proliferation of transformed cells *in vitro* [18]. Like BAFF, APRIL is also a member of the TNF family, with soluble APRIL and BAFF sharing ~30% sequence identity [21]. Unlike BAFF, the soluble form of which can be cleaved at the cell surface [19], overexpression of APRIL in HEK 293T cells indicates that APRIL is processed intracellularly in the Golgi apparatus prior to secretion [59]. BAFF and APRIL can also combine to form heteromers, which have been detected in the sera of patients with rheumatic diseases [60,61]. Heteromers can form either with two APRIL molecules and one BAFF molecule (known as BAA), or one APRIL molecule with two BAFF molecules (known as ABB), the latter of which has been crystallized [62].

Receptor expression and interactions

BAFF binds its three receptors with different affinities: it binds most strongly to BAFF-R, followed by TACI, and binds (monomeric) BCMA rather weakly [63,64]. APRIL

is the preferred ligand of BCMA, whereas TACI binds to BAFF and APRIL with equal affinity [63–65]. BAFF signaling through BAFF-R uses the NF-κB and PI3K pathways [66–68], whereas APRIL signals through the NF-κB pathway following binding to BCMA and TACI [25–27]. APRIL also binds to HSPG both in the extracellular matrix and on the surface of tumor or other cells [29–32], triggering APRIL multimerization and enabling signaling via TACI [32,44,69]. The heteromeric forms of BAFF and APRIL have distinct receptor binding specificities: both ABB and BAA bind to BCMA and TACI, but only ABB binds to BAFF-R (with a weaker affinity compared with BAFF – BAFF-R binding) [62].

BAFF-R, BCMA and TACI are expressed by B cells at various stages of maturation and differentiation [28]. BAFF-R is already expressed by transitional B cells in the BM, albeit at lower levels than on mature B cells, such as naïve and memory B cells [70]. Notably, BAFF-R expression by short-lived plasma cells is also reduced compared with transitional B cells, and is absent from long-lived BM plasma cells, suggesting that its expression may decline as B cells progress towards terminal differentiation [28]. Both BCMA and TACI are expressed by memory B cells and tonsillar germinal center B cells [28,71], and in one study TACI was also detected on a subpopulation of CD27-naïve B cells that expressed activation markers such as CD25 and CD80, suggesting that TACI expression is induced upon B cell activation [28]. While BCMA is expressed by long-lived tonsillar and BM plasma cells, the expression of TACI by tonsillar plasma cells is less clear, with some investigators detecting it [28,71], and others being unable to identify its expression in this cell type [32].

Cellular expression

BAFF mRNA was initially detected in human peripheral blood mononuclear cells (PBMCs) within the spleen, lymph nodes, and BM [19,20], and BAFF protein can be found on the surface of cells of myeloid origin [20]. Expression of BAFF can be induced *in vitro*, in response to granulocyte-colony stimulating factor (G-CSF), interferon-γ (IFNγ), type I IFN, CD40-ligand, lipopolysaccharide or interleukin-10 (IL-10), in both human cell lines of myeloid origin, and cells isolated from human peripheral blood (macrophages, dendritic cells [DCs] and neutrophils) [20,37,56,72]. The upregulation of low levels of BAFF transcription has also been observed in T cells following T cell receptor stimulation [73]. Together, these initial findings have led to the perception that BAFF is primarily produced by cells of myeloid lineage; however, investigations in BAFF-deficient BM chimeric mice and mice immunized with T-dependent antigen indicate that BAFF is also expressed by non-hematopoietic cells, such as stromal cells [74].

Early studies detected APRIL mRNA expression in tumor cell lines and human cancer cells of colon, thyroid, and lymphoid origin [18]. It has since been shown that APRIL is expressed by a number of myeloid-derived cell types including BM granulocytes [45], megakaryocytes [75,76], eosinophils [77] and osteoclasts [78,79], and by dendritic cells following exposure to IFNα, IFNγ or CD40L [37]. APRIL expression is induced during hematopoiesis in the BM. Consistent with the capacity of the BM to sustain long-term survival of plasma cells, APRIL expression is at its highest in immature myeloid cells within the BM [45]. As with BAFF, APRIL expression is not limited to cells of myeloid origin, with several studies detecting its expression in epithelial cells of the gut [80,81], tonsil [32], breast [82], and skin [83]. APRIL expression may also be induced in cell cultures of primary keratinocytes in response to various toll-like receptor agonists [32].

Physiological role in immunity

In vivo studies in BAFF-deficient mice have shown that BAFF signaling through BAFF-R is critical for the differentiation of immature B cells to mature B cells starting at the T1 stage, and for the survival of mature B cells in subsequent stages [23,33–36]. A recent study has reported a distinct subset of TACI-expressing transitional B cells in wild type mice [84]. This subset is markedly expanded in BAFF- transgenic mice and is characterized by an activated phenotype expressing activation-induced cytidine deaminase (AICD) and T-bet. *Ex vivo* stimulation of these cells produces class-switched autoantibodies, suggesting a potential role for TACI on transitional B cells and humoral autoimmunity in high BAFF settings. BAFF also appears to have a role in mature B cell responses; *in vitro* studies indicate that, in the presence of IL-10 or transforming growth factor-β, BAFF can induce CSR of naïve B cells to an IgA isotype [37], and *in vivo* mouse studies have confirmed that BAFF induces CSR to IgG and IgA via interaction with either BAFF-R or TACI [38,80]. The role of BAFF in the establishment of LLPCs is not clear; while BAFF has been shown to support the survival of BM LLPCs *in vitro* and *in vivo* [39,40], plasmablast transfer experiments indicate that establishment of a plasmablast population in the BM is not impaired in BAFF-knock out (Ko) mice, suggesting that BAFF is not critical for this process [43].

BAFF plays a part in T cell responses. Through its binding to BAFF-R, BAFF is able to activate sub-optimally stimulated T cells [73,85,86], but impaired BAFF-BAFF-R binding leads to prolonged allograft survival in mice [87]. BAFF overexpression has been shown to augment

type 1 T helper (Th1) responses in BAFF-transgenic (Tg) mice [88], and BAFF signaling through BAFF-R promotes the accumulation of follicular Th (Tfh) cells, autoantibody production, and IFNγ production in BCMA-deficient, lupus-prone mice. Furthermore, within the germinal center (GC), Tfh cells have been shown to provide a local source of BAFF, and are required for efficient selection of high affinity GC B cells clones [89]. This evidence supports the hypothesis that in SLE patients with high BAFF, autoreactive B cells experiencing high affinity BCR engagement may be rescued and retained during affinity maturation due to local BAFF production. Elevated levels of Tfh cells expressing BAFF-R but lacking BCMA were observed in SLE patients [90]; a result that is interesting in light of the observed correlation between circulating Tfh cells and disease activity in SLE patients [91].

In addition to its role in immune activation, BAFF may also play a part in regulation of the immune response. Exposure to BAFF *in vitro* and *in vivo* has been shown to upregulate the expression of the immune suppressive cytokine IL-10 by B regulatory cells in a TACI-dependent manner, and IL-10 expression is abrogated by inhibition of BAFF with TACI-Ig [92,93]. Interestingly, transient increases in cell numbers from various B cell subsets have been observed clinically in patients treated with BAFF inhibitors [94–96]. This effect may reflect a reduced regulatory B cell response as a result of the inhibition of BAFF; however, further study would be needed to confirm this. Similarly, TACI may also possess some immune regulatory properties, as evidenced by TACI-Ko mouse models, which show increased B cell numbers compared with wild-type mice [97]. Studies of collagen-induced arthritis (CIA) in mice indicate that APRIL may have a similar regulatory role in humoral immunity: APRIL-Tg mice had reduced disease severity and lower autoantibody titers compared with control mice upon CIA induction [98]. However, to what extent APRIL transgene expression in T cells reflects a physiological situation remains an open question, especially in light of the observation that the incidence of CIA in APRIL-Ko mice is decreased, rather than increased [99]. More studies are warranted to determine under which conditions APRIL could stimulate or dampen inappropriate immune responses.

As with BAFF, APRIL is a key player in the humoral immune response, although it appears to act at a later stage, modulating the function and survival of antigen-experienced B cells [23,33–36]. Indeed, APRIL-deficient mice do not display significant differences in immune system development compared with wild-type mice [100]. APRIL is able to induce CSR of naive B cells to IgA or IgG in the presence of IL-10 or TGFβ *in vitro* [37], and APRIL-deficient mice have reduced serum levels of IgA and impaired IgA antibody responses to T-dependent and type 1 T-independent antigens [99,101]. Furthermore, levels of IgM are increased in APRIL-Tg mice, which display both elevated T-dependent IgM responses and type 2 T-independent IgM and IgG responses [102]. Although both BAFF and APRIL play a role in CSR, findings from a study investigating the effects of both proteins on activation-induced cytidine deaminase (AID), an enzyme on which CSR is dependent, suggest that BAFF and APRIL induce CSR in murine B cells by different mechanisms. Whereas APRIL increases the expression of both AID and the transcription factor HoxC4, which induces AID expression, BAFF only upregulates expression of AID [41]. The differential roles of BAFF and APRIL in CSR are also highlighted in another study in which BAFF plus IL-10 was required for the differentiation of IgG plasmablasts, but IgA plasmablast differentiation was dependent on APRIL [42]. This same study found that the binding of APRIL to CD138 on DCs from SLE patients induced both CSR to IgA and plasmablast differentiation.

Numerous studies have demonstrated that APRIL is important for maintenance of the plasma cell pool. APRIL has been shown to promote the survival of LLPCs in mouse BM [39,40,45,77,103], where it provides signals that are critical for the establishment of an IgG-secreting plasmablast reservoir [43]. APRIL mRNA has also been identified in mouse lymph nodes in response to alum-precipitated protein, where higher expression correlated with the presence of more mature plasma cells [104]. *Ex vivo* studies further indicate that APRIL is critical for the survival of human plasma cells in MALT [32,45,105] and the small intestine [80,106]. Furthermore APRIL, as well as BAFF, has been shown to promote the differentiation of naïve B cells into LLPC [107], and the differentiation and proliferation of human memory B cells into plasmablasts [46], indicating that it has a role in immune activation as well as survival. Notably, development and maintenance of the BM plasma cell pool *in vivo* can be driven by either BAFF or APRIL, and therefore blockade of both of these cytokines is required to prevent plasma cell accumulation and survival [29,39].

Further to its direct role in antibody-mediated responses, APRIL may also contribute to T cell-mediated immunity. Transgenic mice studies suggest that APRIL may be involved in T cell survival [102], and APRIL has been shown to induce B cell antigen-presentation *in vitro* in murine splenic B cells [44,108].

Little is known about the physiological role of BAFF-APRIL heteromers. On the one hand, it appears certain that when BAFF is included within a heteromer complex it is markedly less active in terms of activating BAFF-R and maintaining B cell homeostasis than when it is not. In this respect, heteromer formation could be a

mechanism to down-regulate BAFF activity. On the other hand, both ABB and BAA seem competent to activate TACI and BCMA, and might have specific agonist actions on these receptors [62].

The role of BAFF and APRIL in autoimmune disease: Preclinical evidence

The involvement of BAFF and APRIL in the pathogenesis of autoimmune diseases has been the subject of extensive research. Preclinical evidence is primarily derived from mouse models in which BAFF, APRIL, or their receptors are either impaired or deleted, or overexpressed as transgenes.

BAFF overexpression in the mouse induces B cell-derived autoimmune diseases comparable to SLE and IgAN in humans. Lupus-like disease manifestations that are observed in BAFF-Tg mice include increased anti-dsDNA and anti-nuclear autoantibody (ANA) production, increased renal Ig complex deposition, and raised serum IgA, IgG and IgE levels [109,110]. IgA nephritis-like manifestations such as increased mesangial IgA deposits and raised levels of circulating aberrantly glycosylated IgA coinciding with nephritis have also been observed [13]. Interestingly, a number of investigations suggest that BAFF alone is not sufficient to drive lupus-like disease; a study comparing the insertion of the BAFF Tg into non-autoimmune-prone mice versus autoimmune-prone mice found that only the latter developed fulminant renal pathology [111]. Similarly, when BAFF-Tg was introduced into SLE-resistant mouse models, a lack of significant renal immunopathology or active autoimmune disease was noted, even though IgG autoantibody serum levels were increased [112]. BAFF deficiency in New Zealand Mixed (NZM) spontaneous mouse models of SLE also resulted in disease attenuation but not abrogation [113]. Although these animal studies suggest a strong role for BAFF in the pathogenesis of antibody-mediated autoimmunity, they imply that other factors are required for the development of full-blown autoimmune disease. Notably, T cell-deficient BAFF-Tg mice develop an SLE-like disease that is essentially the same as that observed in BAFF-Tg mice with functional T cells, suggesting that BAFF-mediated autoimmunity develops in a T-independent manner [114]. In one study, the SLE-like symptoms observed in BAFF-Tg mice were totally abrogated in the absence of TACI in the hematopoietic compartment, without extensive loss of B cells [115], suggesting that TACI activation, and not B cell activation in general, is responsible for auto-antibody production. If this also applies to clinical SLE, specific inhibition of TACI might represent an alternative to ligand inhibition. Also, inhibition of both TACI ligands would be predicted to reduce the symptoms of SLE more efficiently than inhibition of a single ligand. In contrast, a study using BAFFR-Ko, TACI-Ko, BCMA-Ko NZM2328 mice found that any single BAFF/APRIL receptor was dispensable for the development of SLE [116]. During a subsequent study conducted by the same group using NZM2328 mice deficient in BAFF/APRIL receptor pairs, the authors concluded selective targeting of BAFFR plus TACI or BAFFR plus BCMA may be an efficacious approach [117]. These findings show that the role of BAFF/APRIL receptors is more complex than previously thought, although compensatory mechanisms potentially taking place during life-long deficiency of the receptor(s) cannot be excluded.

Although its role has been less extensively studied in animal models, there is preclinical evidence to support a role for APRIL in antibody-mediated autoimmunity. APRIL mRNA and protein expression is increased in the BM of spontaneous mouse models of SLE compared with control mice [118], and administration of anti-APRIL antibody to mouse models of IgAN results in decreased disease activity (as evidenced by reduced IgA serum levels and reduced glomerular IgA complex deposition) [119]. Studies of APRIL in mouse models of CIA have reported conflicting findings on the effect of APRIL on autoantibody production and arthritis severity. Whereas one group found that IgG2a autoantibody levels were significantly reduced following the subjection of APRIL-deficient mice to CIA [99], another group demonstrated that the severity of CIA was reduced in APRIL-Tg mice alongside a decline in autoantibodies and immune complex deposition, consistent with a protective effect of APRIL against CIA [98]. Caution should be applied when interpreting these findings, however, since the APRIL transgene in this model was controlled by a T cell-specific promoter, which is not consistent with the known pattern of APRIL expression [102]. Clinical evidence supporting a role for APRIL in human antibody-mediated autoimmune diseases is more compelling, and is discussed below.

The role of BAFF and APRIL in autoimmune diseases: Clinical evidence

SLE

Shortly after its identification and characterization as a B cell-stimulating cytokine, elevated levels of functional soluble BAFF were found in the sera of patients with SLE compared with controls [4]. Increased expression of BAFF mRNA has also been observed in peripheral blood leukocytes, and increased expression of the membrane-bound form has been found in PBMCs from patients with SLE [5,6]. Numerous subsequent studies have confirmed these findings and the presence of high serum levels of BAFF in patients with SLE is now very

well-established [1–3]. Several other studies of patients with SLE have detected a correlation between increased levels of serum BAFF and raised autoantibody levels, specifically anti-ds-DNA [4,5,51] and anti-Smith antibodies [3]. However, one recent study found no association between BAFF serum levels and anti-ds-DNA autoantibody titers in patients with SLE; although the authors suggest that the disrepancy between this finding and previous reports may be due to different anti-ds-DNA detection methods [1]. Indeed, the link between BAFF and anti-ds-DNA has been demonstrated in mice, where BAFF overexpression leads to the maturation of anti-ds-DNA B cells [120].

Post-hoc analyses of the randomised phase III clinical studies, BLISS-52 and BLISS-76, showed BAFF levels ≥2 ng/ml at screening to be an independent prognostic factor for increased risk of moderate and severe lupus flare [49]. Other SLE markers, including raised autoantibody levels, were also associated with BAFF ≥2 ng/ml [121]. Similarly, a *post hoc* analysis of the phase II/III APRIL-SLE study also found that BAFF levels greater than median at baseline correlated with increased risk of British Isles Lupus Assessment Group (BILAG) A or B flare in the placebo group [122]. Other studies investigating the association between BAFF serum levels and SLE disease activity, however, have yielded mixed results. For example, some investigators have reported correlations between serum BAFF and SELENA–SLEDAI (Safety of Estrogen in Lupus Erythematosus National Assessment SLE Disease Activity Index) score [48] and the Mexican (Mex)-SLEDAI score [2], while others have reported a lack of correlation between BAFF and SLEDAI [1,5] or the Systemic Lupus Activity Measure (SLAM) [4]. It is feasible that the use of different scoring systems to measure disease activity may have led to the discrepancy between these findings; however, two different studies both investigating the association between BAFF and the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI) have reported conflicting outcomes [3,4]. These different observations may also reflect the different methods used to detect BAFF; for instance, one group demonstrated that increased BAFF mRNA levels in PBMCs correlate better with disease activity than serum BAFF protein [6]. Furthermore, it is feasible that the use of BAFF to predict disease outcomes needs to focus on more specific manifestions of SLE rather than general disease activity, for example renal pathology, since BAFF levels are higher in patients with active lupus nephritis (LN) compared with controls [123].

Similar observations have been made for APRIL in SLE, with multiple investigations reporting raised levels of soluble APRIL in the sera of patients with SLE compared with healthy individuals [7–10]. In addition to the APRIL protein, an association between SLE and a polymorphism at codon 67 of the *APRIL* gene has also been demonstrated [124,125]. There are conflicting reports for correlations between APRIL serum levels and autoantibodies in patients with SLE. Some investigators have noted a weak correlation between elevated APRIL levels [7] and anti-ds-DNA antibodies, while others have suggested that an inverse correlation exists between the two [8,9]. Like BAFF, APRIL levels in sera appear to be linked to SLE disease activity. Although inverse correlations have been observed between serum APRIL levels and SLEDAI scores [8,9], a significant positive association has been noted with the BILAG index overall [10], as well as specific manifestations of SLE, including the BILAG musculoskeletal score [7,10], and the BILAG cardiorespiratory score [10]. Associations have also been observed between both serum APRIL levels and renal mRNA expression, and renal disease severity in patients with LN, with raised APRIL levels predictive of resistance to immunosuppressive therapy [50].

Although both BAFF and APRIL are undoubtedly raised in the sera of patients with SLE, a relationship between co-expression of the two molecules is yet to be clearly determined. In one study, a negative correlation between BAFF and APRIL serum levels was observed [9]. A separate study found no correlation between serum BAFF and APRIL, but mRNA levels of the two cytokines was paralleled in the blood, leading the authors to suggest that serum levels of the BAFF and APRIL proteins may be differentially regulated [8]. Another investigation indicated that abberant activation of B cells in patients with SLE contributes to raised levels of both cytokines, which may in turn lead to a vicious circle resulting in the further up-regulation of BAFF and APRIL expression [126]. Furthermore, in the same *post-hoc* analysis of the APRIL-SLE study that found an association between BILAG A or B flare risk and BAFF, a more pronounced risk was observed when both APRIL and BAFF were elevated in tandem [127].

IgAN

Several investigators have reported raised levels of BAFF protein in the sera of patients with IgAN compared with controls [11–13]. In one study, an association was found between BAFF serum levels and disease severity, as measured by IgAN markers including renal histopathology, estimated glomerular filtration rate, serum creatinine, circulating IgA1 levels, and mesangial IgA deposition density [11,12]. A number of additional studies have shown that mononuclear cells isolated from the tonsils of patients with IgAN can be induced to express higher levels of BAFF *in vitro* than those from control patients [128–130].

Elevated serum levels of APRIL have also been reported in patients with IgAN. In one study, APRIL levels correlated with IgAN disease activity markers, serum creatinine, and urine protein/creatinine ratio in a subset of patients. Notably, raised BAFF levels in these patients were modest in comparison to those of APRIL [13]. In another study, APRIL protein was significantly higher in the plasma of IgAN patients compared with healthy controls, and increased plasma APRIL levels were associated with more severe clinical manifestations (higher proteinuria and lower glomerular filtration rate). Furthermore, upregulation of APRIL mRNA expression was detected in B cells derived from patients with IgAN and a trend towards increased BCMA and TACI expression compared with controls was also observed [131].

Other antibody-mediated autoimmune diseases

In addition to SLE and IgAN, increased BAFF and APRIL expression has been observed in other rheumatic diseases. Elevated serum levels of BAFF protein have been seen in patients with RA compared with healthy control individuals [17], and a positive correlation has been observed between BAFF and IgM rheumatoid factor titers, as well as anti-cyclic citrullinated peptide autoantibody [52]. The *BAFF-871C>T* polymorphism has also been found to influence the outcome of treatment with the anti-CD20 antibody rituximab in RA [132]. APRIL-producing cells, as well as secreted APRIL, have been detected in the synovial tissues of patients with RA [133], both BAFF and APRIL mRNA expression has been observed in inflamed synovial tissue [134], and an association has been noted between serum BAFF and synovitis [52].

Raised levels of BAFF have been found in the sera of patients with SS compared with controls [14], and shown to correlate with autoantibody levels [53]. Increased APRIL levels have also been detected in the serum of patients with SS, although the investigators in this study found no difference between patients and controls in terms of serum BAFF levels [15]. In another study, increased serum BAFF and APRIL were found to correlate with SS focus score and IgG levels, suggesting a possible association between BAFF and APRIL and SS disease activity [16]. However, a separate investigation revealed that APRIL was absent from the salivary gland lesions of patients with SS [135]. Although these studies have reported somewhat mixed findings, the evidence overall points to a degree of involvement of both cytokines in SS.

In addition to the better-known rheumatic diseases, raised BAFF and APRIL levels have also been detected in patients with the recently recognized condition, IgG4-related disease (IgG4-RD) [136]. The precise role of the two cytokines in the pathogenesis of IgG4-RD is yet to be defined, however, high levels of APRIL-producing macrophages have been detected in IgG4-related kidney disease [137], and inhibition of APRIL has been shown to suppress disease progression in a mouse model [138].

Endogenous BAFF and APRIL deficiency may provide a rationale for targeting BAFF and APRIL in autoimmune disease

Given their critical role in B cell-mediated autoimmunity, targeting BAFF and APRIL in the treatment of diseases such as SLE and IgAN is a rational approach to therapy. Direct inhibition of these two molecules has the potential to prevent engagement of their receptors, BAFF-R, TACI and BCMA, and thus to prevent subsequent activation of B cell-driven mechanisms, such as autoantibody production, that contribute to the pathology of autoimmune diseases.

The potential effects of impaired TACI signaling can be seen endogenously in common variable immunodeficiency (CVID), a disease characterized by hypogammaglobulinemia and recurrent respiratory infections [139].

Mutations in the TACI gene, *TNFRSF13B,* can be found in subsets of patients with CVID at a significantly higher rate compared with healthy individuals. When naïve B cells from such patients are exposed to APRIL *ex vivo*, this does not lead to isotype switching, suggesting that the *TNFRSF13B* mutation leads to impaired APRIL-TACI signalling [140]. A similar observation was made in a study of CVID patients with homozygous *TNFRSF13B* mutations, in which a reduced B cell proliferative response to IgM/APRIL costimlation was observed, as well as defective IL-10-, APRIL- or BAFF-induced CSR [141]. A large analysis of 564 unrelated patients confirmed that two disease-modifying TACI mutations, C104R and A181E, are significantly enriched in CVID, although these were neither necessary nor sufficent to cause the disease [142].

Genetic alterations in the BAFF-R gene, *TNFRSF13C,* have also been found in CVID, including three polymorphic variants that result in amino acid substitutions, one of which, P21R, interferes with BAFF-R self-association and function, and contributes to CVID [143,144]. One investigation reported two human siblings each carrying a homozygous deletion in *TNFRSF13C* that deletes the transmembrane domain of BAFF-R, leading to lack of BAFF-R expression. These patients had a B cell maturation arrest at the transitional stage, lower levels of serum IgG and IgM, but normal IgA levels, leading the investigators to conclude that abrogation of BAFF-R leads to an altered immunological phenotype but not necessarily to full-blown immunodeficiency [145].

Taken together, these findings suggest that impaired TACI or BAFF-R signalling can lead to hypogammaglobulinemia. Although this outcome is clearly not desirable

when it manifests as CVID, these observations nevertheless imply that inhibition of TACI and/or BAFF-R signaling has the potential to block the processes that lead to autoantibody production in patients with humoral autoimmune disease.

In addition to studies in CVID, recent investigations have revealed the existence of soluble forms of TACI and BCMA that are elevated alongside raised BAFF and APRIL in patients with SLE. Soluble TACI (sTACI) has been shown to bind BAFF and APRIL, whereas soluble BCMA (sBCMA) only binds APRIL. sTACI and sBCMA act as decoy receptors, blocking engagement between BAFF and APRIL and membrane-bound TACI and BCMA, resulting in inhibition of NF-κB signaling by both receptors, and subsequent inhibition of B cell survival *in vitro* [146,147]. These observations serve to support the rationale for blockade of BAFF/APRIL engagement with their receptors in order to reduce their potential to promote the survival of pathogenic B cells.

Preclinical investigation of BAFF/APRIL antagonists in animal models of autoimmune disease

As part of the research to characterize the roles of BAFF and APRIL in immunity and pathogenesis, the effects of blocking the two cytokines have been investigated in animal models of autoimmune disease. These include primarily NZM mice and NZB/W F1 mice, which spontaneously develop characteristics of SLE.

In one study, treatment of NZB/W F1 mice with a BAFF-R fusion protein blocked BAFF signaling, resulting in reduced SLE disease activity [67]. In another study, BAFF-deficiency in NZM.*Baff*−/− mice reduced total Ig and autoantibody levels up to 4–6 months of age, after which time autoantibody levels increased, despite the complete absence of BAFF [113]. In these autoimmunity-prone BAFF-deficient mice, proteinuria and mortality rates were much decreased, indicating that BAFF inhibition may be able to attenuate disease severity, while not offering complete protection from autoimmunity.

Treatment of NZB/W F1mice with anti-APRIL monoclonal antibodies (mAbs) had a modest effect on disease progression and mortality [118]. Anti-ds-DNA IgG were unaffected and anti-chromatin levels were modestly decreased. By contrast, a previous study reported an inverse correlation between APRIL serum levels and anti-ds-DNA titers in patients with SLE [8]. Similar results have been observed in IgAN mouse models, in which treatment with anti-APRIL antibodies reduced disease progression, lowered serum IgA levels and reduced glomerular deposition of immune complexes [119].

A number of studies suggest that dual inhibition of BAFF and APRIL may provide more pronounced pharmacodynamic (PD) effects than inhibition of either molecule alone and may also be efficacious in SLE models. In an investigation comparing BAFF blockade by the fusion protein BAFF-R-Ig with BAFF/APRIL blockade by the TACI-Ig fusion protein, both techniques led to a reduction of B cell numbers and prolonged survival in NZB/W F1 mice, but only TACI-Ig led to reduced IgM levels, inhibition of the IgM response, and reduced plasma cell numbers in both spleen and BM in NZM2410 mice [148]. This is consistent with a separate investigation in which TACI-Ig treatment led to reduced survival of plasma cells [40]. Therefore, TACI-Ig may be a better option for disease mediated by short-lived or LLPC. On the other hand, use of either BAFFR-Ig or TACI-Ig may cause immunosuppression due to the mechanisms of action. Clear understanding of the BAFFR-Ig or TACI-Ig drug exposure, PD and disease treatment effect may help to identify the dose range that will offer the best risk benefit balance. When BAFF/APRIL-Ko mice were compared with BAFF-Ko mice, impairment of both BAFF and APRIL led to a more pronounced reduction in BM plasma cells than impairment of BAFF alone [149]. No increased modulation of disease phenotype was noted with dual BAFF/APRIL deletion versus deletion of BAFF alone, prompting the investigators to question whether the efficacy achieved by the clinical targeting of both molecules would be offset by the potentially detrimental effects of stronger immunosuppression. In terms of the clinical application of BAFF and/or APRIL inhibition, this concern is valid and warrants careful investigation. However, it cannot be excluded that compensatory mechanisms potentially taking place during a life-long BAFF- and APRIL-deficiency might differ from those achieved upon pharmacological inhibition in BAFF- and APRIL-sufficient animals. Our group has recently presented early findings that show that pharmacological dual inhibition of both BAFF and APRIL with TACI-Fc was able to completely prevent disease progression in NZB/W F1 mice, with the onset of nephritis, autoantibody production and glomerular immune complex deposition arrested [47]. By contrast, inhibition of BAFF alone with BAFF-R-Fc was only able to delay, but not prevent indefinitely, the development of SLE. It is unlikely that these differences could be explained by the activation of membrane-bound BAFF or APRIL by TACI-Fc [150]. Interestingly, *in vitro* studies have shown that BAFF/APRIL/APRIL heteromers can be blocked by TACI-Ig and BCMA-Ig, but not by BAFF-R-Ig or an anti-BAFF antibody [61,62], suggesting that dual inhibition of BAFF/APRIL by TACI-Ig may be the only effective method by which to block the BAFF/APRIL heteromers that are present in autoimmune diseases [60,61].

Clinical investigation of BAFF and APRIL antagonists in SLE and other humoral autoimmune diseases

Agents targeting BAFF signaling alone and BAFF/APRIL signaling together have both been subject to clinical investigation. While BAFF signaling is targeted through direct blockade of BAFF, BAFF/APRIL signaling inhibition has been achieved using a soluble form of their shared receptor, TACI. Soluble forms of BCMA have not yet been explored in a clinical setting, probably because BCMA has a higher affinity for APRIL than BAFF, whereas TACI binds both molecules with similar affinity [63,64].

BAFF only inhibition

During recent years, a number of BAFF-targeting agents have been explored in the treatment of SLE. Three of these, belimumab (GlaxoSmithKline), blisibimod (Anthera) and tabalumab (Eli Lilly), have reached phase II/III clinical investigation.

Belimumab. Belimumab (Benlysta®) is a recombinant, fully human $IgG_{1\lambda}$ mAb that binds soluble BAFF, blocking its interaction with BAFF-R, TACI and BCMA [151]. An initial randomized phase I study in patients with mild-to-moderate SLE confirmed the safety and tolerability of belimumab and demonstrated its biological activity through significant B cell reductions compared with placebo [152]. A subsequent phase II study in 449 SLE patients failed to meet its co-primary endpoints of improved SELENA-SLEDAI scores at week 24 and delayed time to first flare up to week 52; however, a *post hoc* analysis revealed improved disease activity with belimumab in a subgroup of patients with serologically active disease (ANAs ≥ 1:80 and/or anti-ds-DNA antibodies ≥30 IU/mL) at week 52. Reductions in naïve, activated and plasmacytoid CD20+ B cells, as well as anti-ds-DNA antibody titers were also observed [153]. Following on from this positive finding, two large randomized phase III studies, BLISS-52 (n = 867) and BLISS-76 (n = 819), examined belimumab 1 or 10 mg/kg compared with placebo for 52 weeks and 76 weeks, respectively, in patients with seropositive (ANA+ or anti-ds-DNA+) SLE [152,154]. While BLISS-52 demonstrated significant improvements in the SLE Responder Index (SRI) at both doses [154], improvements were only seen with the higher belimumab dose in BLISS-76 [155]. No significant imbalance of adverse events (AEs) were reported between treatment arms in any of these studies. Based on these findings, belimumab 10 mg/kg was approved in 2011 by both the FDA and the EMA as an add-on therapy for patients with active, autoantibody-positive SLE receiving standard treatment.

Since receiving approval, the subcutaneous (s.c.) administration of belimumab in patients with SLE has also been investigated in the phase III BLISS-SC trial (n = 839), which demonstrated increased SRI-4 response at week 52 with belimumab 200 mg versus placebo and a similar safety profile [156]. At the time of writing, several more phase III studies investigating belimumab in autoimmune diseases are either ongoing or planned. These include long-term extension studies following BLISS-52 and BLISS-76 (NCT00712933), a continuation of BLISS-SC in Northeast Asian and Japanese patients (NCT0159762), a phase III study in Northeast Asian patients with SLE (NCT01345253), a phase III study in patients with LN (NCT01639339), and a phase II/III study in patients with refractory idiopathic inflammatory myositis (NCT02347891).

Blisibimod. Unlike belimumab, which is reported to target soluble BAFF, blisibimod is a peptibody that binds both the soluble and membrane-bound forms of BAFF [157]. Initial phase I studies confirmed the safety of blisibimod in patients with mild SLE, and reductions in naïve B cell numbers suggested a pharmacodynamic effect [94]. Subsequently, a phase IIb study of s.c. blisibimod (100 or 200 mg once-weekly [QW], or 200 mg every 4 weeks [Q4W]) compared with placebo in patients with seropositive SLE (PEARL-SC; n = 547), failed to meet its primary endpoint of improved SRI-5 response at week 24 in the pooled dose group, but showed significant improvements with the highest dose [158]. Significant reductions in anti-ds-DNA antibody titers, complement C3 and C4, and B cell numbers were observed with blisibimod compared with placebo. No imbalances in AEs were reported in either the phase I or phase II blisibimod studies [94,158]. At the time of writing, two randomized phase III studies in patients with seropositive SLE, CHABLIS-SC1 (NCT01395745) and CHABLIS7.5 (NCT02514967), were ongoing and planned, respectively, and a further phase II/III study in patients with IgAN, BRIGHT-SC (NCT02062684) was also ongoing.

Tabalumab. Tabalumab is a human IgG_4 mAb that, like blisibimod, binds both forms of BAFF [159]. The biological activity, safety and tolerability of tabalumab was initially characterized in randomized phase II trials in patients with RA. These studies showed that there was no meaningful difference in AEs with tabalumab compared with placebo, however, treatment with tabalumab led to transient increases in total B cells, as well as naïve and memory B cells [95,96]. Efficacy signals in patients with RA were mixed, with primary efficacy endpoints being met in only one out of the three phase II studies [95,96,160]. Two pivotal phase III studies, ILLUMINATE-1 (n = 1164) and ILLUMINATE-2 (n = 1124), assessing tabalumab in patients with moderate-to-severe SLE were done. In ILLUMINATE-1, tabalumab did

not achieve the primary endpoint (SRI-5), whereas in ILLUMINATE-2, the higher frequency dosing regimen of tabalumab (120 mg every 2 weeks) met this endpoint [161,162]. In response to these results, the sponsor Eli Lilly announced in 2014 that development of tabalumab would be discontinued due to failure to meet expectations of efficacy [163].

BAFF and APRIL dual inhibition

Atacicept. To date, the most extensively investigated compound targeting soluble and membrane-bound forms of both BAFF and APRIL is atacicept. Atacicept is a fully human, recombinant soluble fusion protein containing the extracellular ligand-binding domain of TACI fused to a modified Fc portion of human IgG1, which is designed to be administered via s.c. injection. The safety, tolerability and biological activity of atacicept were confirmed in phase Ib placebo-controlled dose escalation trials in patients with mild-to-moderate SLE [164,165]. Atacicept was subsequently investigated in the treatment of RA in two phase II studies, which compared atacicept doses up to 150 mg with placebo in patients for whom TNF-antagonist treatment had failed (AUGUST-1; $n = 256$), and in TNF-antagonist-naïve patients (AUGUST-2; $n = 311$) [166]. Both studies failed to meet their primary endpoints of 20% improvement in disease severity according to ACR criteria at week 26, but were able to further confirm the biological activity of atacicept by showing dose-dependent reductions in IgM, IgA and IgG levels, as well as absolute reductions in mature B cells and plasma cells relative to baseline at week 26. An additional exploratory phase II study (AUGUST-3; $n = 27$) demonstrated reduced median Ig levels at week 32 compared with baseline, but showed no additional clinical benefit of adding atacicept to rituximab [167].

The APRIL-SLE phase II study, which examined atacicept 75 or 150 mg compared with placebo in patients with moderate-to-severe SLE, yielded more promising efficacy results [122]. In *post hoc* analyses, atacicept 150 mg weekly (add-on to standard of care) was associated with a reduction in risk of flare (defined as a BILAG A or B flare, with discontinuations imputed as flares). However, this treatment arm was discontinued prematurely following a second infection-related death, in accordance with the recommendation from the Independent Data Monitoring Committee. The primary endpoint, evaluating the risk of flare in patients treated with atacicept 75 mg weekly versus placebo (add-on to standard of care), was not met. Both atacicept doses were also associated with reductions in B cells, plasma cells, total Ig levels and anti-ds-DNA antibodies, and increases in complement C3 and C4 levels. As might be expected given the PD effect of atacicept on the immune system, the most frequently reported serious AE noted in the APRIL-SLE study was infection. However, serious infection occurred at a similar incidence with atacicept 75 and 150 mg and placebo (8.3%, 7.6% and 7.1%, respectively) [122], and at a comparable rate to that reported with the BAFF-only inhibitor belimumab 1 and 10 mg/kg in the BLISS 76 (7.0 and 7.3%, respectively) [155] and BLISS-52 (8% and 4%, respectively) [154] studies. The majority of AEs with atacicept were mild or moderate. The two fatalities (1.4%) that were reported in the atacicept 150 mg treatment arm were caused by acute respiratory failure secondary to possible leptospirosis, and pneumococcal pneumonia and alveolar hemorrhage secondary to lupus [122], but neither were associated with hypogammaglobulinemia. Although inter-study comparisons should be treated with caution, similar numbers of deaths occurred in the belimumab-treatment groups in the BLISS-76 and BLISS-52 trials (3 [0.6%] and 6 [1.0%]), with 3 of the deaths occurring in BLISS-52 attributed to infection [154,155].

A phase II/III study assessing the safety and efficacy of atacicept 150 mg in patients with active LN receiving newly initiated corticosteroids (CS) and mycophenolate mofetil (MMF), was stopped after the enrollment of six patients due to increased infections associated with an unexpected decline in serum IgG. A number of factors likely contributed to these adverse events [168]. These are discussed in further detail in a review by Cogollo et al. [169], however, in summary the IgG decline began 2 weeks prior to first administration of atacicept, when CS and MMF therapy was initiated, and continued after the addition of atacicept. Since these standard therapies have been linked to hypogammaglobulinemia in other studies, they may have contributed to the reduced IgG observed in the atacicept study [169]. Subsequent to the discontinuation of the phase II/III study, a phase Ib study examining the safety and tolerability of atacicept in patients with LN receiving a stable regimen of MMF with glucocorticoids was undertaken. This trial was also terminated prematurely, following the death of the first patient enrolled. The post-mortem examination revealed that the cause of death, cardiac failure due to an acute thrombus in the left anterior descending artery, occurred in the setting of pre-existing diffuse coronary artery disease associated with cardiac ischemic changes of at least several weeks' duration, prior to the administration of atacicept.

The safety and tolerability of atacicept has now been studied in >1000 patients. Further evaluation of the benefit risk profile of ataciept in patients with moderate SLE is being evaluated in the phase IIb clinical study, ADDRESS II (NCT01972568). The primary endpoint of ADDRESS II is the proportion of patients achieving reduced disease activity (defined by meeting the SLE Responder Index Criteria; SRI), with atacicept 75 or 150 mg versus placebo,

at 24 weeks. At the time of writing, enrollment was complete, with the primary analysis due to be carried out in 2016. A long-term extension study of ADDRESS II will assess the long-term safety, effects on disease activity, and PD effects such as levels of serum Ig, B cells, and plasma cells. The study will also examine the correlation between baseline serum levels of BAFF and APRIL with treatment response (NCT02070978). Based on its proven pharmacodynamics effects, future clinical exploration of atacicept in other antibody-mediated autoimmune diseases is warranted.

RCT-18. Another compound targeting both BAFF and APRIL is the TACI *RCT-18*-Fc recombinant fusion protein, RCT-18, which contains a longer TACI fragment than atacicept. RCT-18 was recently assessed in a randomized phase I, first-in-man study in patients with RA ($n = 28$) [170]. Compared with placebo, RCT-18 was found to be well-tolerated when administered s.c. at doses up to 540 mg, with IgM reductions achieved at the highest dose. However, no difference between RCT-18 and placebo in terms of IgG or IgM response profiles was found. RCT-18 has also been investigated in a small phase I study in which patients ($n = 12$) were randomized 3:1 to receive RCT-18 (180 mg s.c. QW) for 4 weeks or placebo, and observed for 84 days [171]. The investigators reported reductions in IgM and IgA levels, but increases in naïve and memory B cell counts after administration. A higher rate of infection was also observed amongst patients receiving RCT-18, leading the investigators to conclude that a lower dose should be considered for future studies.

APRIL and BAFF as predictive biomarkers

Post-hoc analyses of the BLISS study have suggested a link between treatment response to belimumab and increased baseline serum levels of BAFF. Response parameters were numerically higher in patients with BAFF ≥2 ng/ml compared with those with BAFF <2 ng/mL [121], suggesting that baseline BAFF may be a useful measure for predicting response to belimumab treatment in the future. Similarly, a *post-hoc* analysis of the APRIL-SLE study has indicated that treatment effect size was greatest in a subgroup of patients with high baseline serum levels of both BAFF and APRIL, suggesting a role for the concurrently increased expression of these cytokines as a predictive biomarker for atacicept [172].

While these observations represent an exciting prospect for the use of APRIL and/or BAFF serum levels as predictive biomarkers, it is worth highlighting that several factors need to be taken into consideration for potential future techniques utilizing the two cytokines to identify patients most likely to respond to belimumab or atacicept treatment. For example, circulating BAFF and/or APRIL are not necessarily active molecules due to their potential to be blocked by soluble decoy forms of BCMA and TACI [146,147]. Furthermore, soluble BCMA and TACI decoy receptor binding has the potential to affect the quantification of BAFF and APRIL levels. Few, if any, studies have assessed whether the measured levels of BAFF and APRIL represent active or inactive cytokines. It is also unclear what proportion of BAFF and APRIL are bound by BCMA, TACI, BAFF-R or HSPGs outside the circulation (e.g. within the BM, MALT or gut) and are therefore not detectable within the serum. Finally, the correlation between treatment response and the relative ratios of BAFF/APRIL homo- and heterotrimers in the circulation may also be an influential factor that warrants further examination.

Conclusion

TNF family members BAFF and APRIL have both overlapping and distinct roles in humoral immunity. Both molecules play key roles in the pathogenesis of diseases with autoreactive B cell involvement, such as SLE, making them excellent candidate targets for new therapies. Although the BAFF inhibitor belimumab is already approved for the treatment of patients with SLE, emerging evidence suggests that targeting both molecules may provide more complete inhibition of the processes involved in autoantibody production. As such, studies are currently ongoing to assess the safety and efficacy of the TACI-Ig, atacicept, in the treatment of SLE, and the results of the phase II ADDRESS II study are likely to be highly relevant to the clinical community.

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Declaration of Interest

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