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BAFF inhibition: a new class of drugs for the treatment of autoimmunity

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Abstract

BAFF (BLyS) and APRIL are TNF-like cytokines that support survival and differentiation of B cells. Recent studies have discovered a role for BAFF in augmenting both innate and adaptive immune responses as well as in collaborating with other inflammatory cytokines to promote the activation and differentiation of effector immune cells. BAFF is an important pathogenic factor in lupus mouse models and BAFF inhibition successfully delays disease onset in these mice, although the responsiveness to BAFF inhibition varies among different strains. These results have led to the development of inhibitors targeting BAFF and APRIL in humans. An anti-BAFF antibody has shown significant but modest efficacy in two Phase III clinical trials for moderately active SLE and other inhibitors are being developed or at early stages of clinical testing.

Keywords

Autoimmunity; Systemic lupus Erythematosus; B cells; BAFF

Introduction

BAFF (B cell activating factor belonging to the TNF family), also known as BLyS (B lymphocyte stimulator) is a vital homeostatic cytokine for B cells that helps regulate both innate and adaptive immune responses [1]. Increased serum levels of BAFF and its homolog APRIL (a proliferation inducing ligand) are found in several autoimmune diseases, and both cytokines can be elaborated in inflammatory sites. The successful use of BAFF/APRIL inhibitors in murine models of autoimmunity [2,3] has led to the rapid development of this class of drugs for clinical testing in humans. The first of these drugs, belimumab, a monoclonal antibody specific for soluble BAFF has demonstrated efficacy in phase III studies of moderately active SLE (R.F. van Vollenhoven, abstract OP0068 presented at EULAR Congress, Rome 2010 and S. Navarra, abstract SAT0204 presented at EULAR Congress, Rome, 2010). A different anti-BAFF antibody that recognizes both soluble and membrane BAFF has exhibited efficacy in phase II studies of rheumatoid arthritis. The dual BAFF/APRIL inhibitor, atacicept (TACI-Ig fusion protein) is undergoing clinical trials in several autoimmune diseases [4-7] and several other antibodies and fusion proteins are in development. In this review we will summarize the physiology of BAFF and its receptors,

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and discuss both its pathogenic role in autoimmunity and its potential as a therapeutic target with a focus on SLE.

BAFF, APRIL and their receptors

BAFF and its homolog APRIL are members of the tumor necrosis factor family and are expressed by monocytes, DCs, neutrophils, basophils, stromal cells, activated T cells, activated and malignant B cells, and epithelial cells [1,8-10]. BAFF binds to 3 receptors, BAFF-R, TACI (Transmembrane activator and calcium modulator ligand interactor) and BCMA (B cell maturation antigen) that are expressed by B cells at various times during their ontogeny [2,11]. BAFF-R is specific for BAFF whereas TACI and BCMA also bind to APRIL [1]. BAFF is mostly cleaved from the cell surface and circulates as a soluble homotrimer that binds to BAFF-R [12]. In contrast, binding of BAFF and APRIL to TACI requires ligand multimerization; BAFF self-associates spontaneously into multimers of twenty trimers whereas APRIL is aggregated on cell surfaces by binding to sulfated proteoglycans [12] (Figure 1).

Receptor signaling

Each of the three receptors has a different pattern of expression and each mediates distinct functions. BAFF-R is expressed on naïve and memory B cells and, through activation of the alternative NF-κB pathway, enhances B cell survival by upregulating anti-apoptotic proteins [13]. BAFF-R ligation also weakly stimulates the classic NF-κB pathway and transduces signals through mTOR and Pim2 that promote protein synthesis and cell growth [14,15]. TACI is expressed on most B cell types after the T2 stage and both TACI and BCMA are expressed on plasmablasts and plasma cells [1,16]. TACI and BCMA signal through the classic NF-κB pathway, as well as through other pathways to counteract apoptosis and to drive class switching [17,18]. An ongoing puzzle is the mechanism for the regulatory role of TACI, with the development of autoimmunity and lymphomas in TACI deficient mice [19].

Splice variants

Of the several splice variants of the cytokines and their receptors, the best characterized is ΔBAFF, a variant that is missing an exon and is inefficiently cleaved from the cell surface. ΔBAFF does not bind either BAFF-R or TACI *in vitro* but limits BAFF availability by forming heterotrimers with full length BAFF. ΔBAFF transgenic mice have a mildly reduced B cell pool, a suboptimal antibody response to T cell dependent antigens and more stringent selection of their B cell repertoire [20,21]. The function of cell surface-expressed ΔBAFF homotrimers is not yet known, nor is it known how differential splicing is regulated. Understanding more about the regulation of expression and function of ΔBAFF is important since a BAFF inhibitor that targets membrane as well as soluble BAFF is in early clinical trials. There is some evidence that signaling through membrane BAFF in monocytes and dendritic cells induces cell activation and expression of inflammatory mediators and costimulatory molecules [22,23]. For this reason, it needs to be determined whether the membrane BAFF inhibitor will interfere with the regulatory role of ΔBAFF, and how it affects the functions of membrane expressed BAFF.

BAFF and BAFF-R are required for naïve B cell survival and selection

BAFF is crucial both for B cell homeostasis and for the regulation of B cell selection. Early transitional (T1) cells with immature rafts are subject to deletion or anergy induction if they receive a signal through the BCR. In the late transitional stage, BCR signaling through maturing rafts upregulates expression of BAFF-R and also generates p100, a substrate for the non-classical NF-ΔB signaling pathway used by BAFF-R [15,24]. Autoreactive B cells

that have downregulated their BCR as a consequence of antigen stimulation at the T1 stage produce less p100, express less BAFF-R and compete poorly for BAFF as they progress to the T2 stage. When B cell numbers and BAFF levels are normal, stringent deletion of autoreactive B cells occurs. However an increase in serum BAFF levels may result in relaxation of B cell selection, with survival of more autoreactive naïve B cells [25,26].

BAFF plays an important role in immune responses to pathogens

Innate immunity

BAFF is produced by myeloid DCs in response to type I interferons (IFNs) [27] and it collaborates with cytokines and toll like receptor (TLR) signals to promote Ig class switching and plasma cell differentiation [28,29]. In SLE, class switching of autoreactive B cells from IgM to more pathogenic IgG is a critical checkpoint in the initiation of clinical disease. Autoreactive B cells in SLE internalize immune complexes or apoptotic material containing nucleic acids that activate TLRs, causing increased expression of the BAFF receptor TACI [28,30]. High serum levels of BAFF may therefore preferentially support the survival and induce class switching of these cells. In support of this notion, marginal zone B cells undergo T-independent class switching in BAFF transgenic mice and secrete autoantibodies that cause mild SLE [30]. Some SLE patients chronically have 3-4 fold increases in serum BAFF levels; this could be due to B cell lymphopenia, increased type I IFNs, or BAFF production from inflammatory sites. It is not yet clear whether this increase in BAFF levels is responsible for aberrant selection or class switching of naïve B cells in SLE and whether such abnormalities can be reversed by BAFF inhibition.

Antibody responses

T cell independent type II responses and T cell dependent IgM responses require the interaction of BAFF with TACI [1]. BAFF also seems to be involved in germinal center responses as BAFF-deficient mice fail to develop a mature FDC network and have small and unstable germinal centers; class switching and somatic hypermutation still occur, but IgG and secondary responses are diminished [31,32]. Although germinal centers are similarly small in BAFF-R deficient mice [31], the FDC defect is not seen, indicating that the interaction of BAFF with TACI is most likely involved in FDC maturation.

Effector B cells

Although memory B cells express BAFF-R [33] survival and reactivation of class switched B cell memory cells is BAFF independent under normal physiologic circumstances [34]. BAFF can however, collaborate with inflammatory cytokines such as IL-21 and IL-17 in the reactivation of memory B cells and their differentiation to plasma cells [35,36]; whether this occurs *in vivo* is not yet known. Surprisingly, BAFF inhibition with either belimumab or atacicept results in rapid expansion of the memory B cell pool in humans [4,5,37]. Whether this is due to homeostatic proliferation of memory B cells or mobilization of cells into the circulation is not yet known.

Plasma cells express TACI and BCMA and their survival can therefore be supported by either BAFF or APRIL that are secreted by stromal cells (BAFF) and dendritic cells (APRIL) within the lymph node or bone marrow microenvironment [38,39]. This means that blockade of both cytokines is required to deplete plasma cells [3,40]. Importantly, dual BAFF/APRIL inhibition is associated with a preferential decrease in IgM and IgA producing plasma cells compared with IgG producing plasma cells. In accord with these findings, BAFF/APRIL inhibition has little effect on circulating IgG levels to recall antigens such as tetanus [4].

Regulatory B cells

Recent work suggests a possible role for BAFF in the maintenance of regulatory B cells that produce IL-10 [41] but this needs to be confirmed; the consequence of chronic BAFF inhibition with respect to this cell population is not known.

Unique functions of APRIL

APRIL does not bind to BAFF-R and therefore is not involved with naïve B cell selection or survival. Class switching to IgA appears to be dependent on the interaction of APRIL with TACI suggesting that APRIL functions in the maintenance of mucosal immunity and serum levels of IgA [42]. APRIL is also essential for the survival of plasma cells in neonatal bone marrow and low expression of APRIL by bone marrow stromal cells in early life may be responsible for the rapid waning of IgG antibodies elicited in infancy [38]. As mentioned above, atacicept that blocks both BAFF and APRIL severely depletes serum levels of IgM, thus ablating early humoral responses to bacteria and viruses and potentially increasing infection risk.

Role of BAFF/APRIL in other leukocytes

BAFF-R is expressed on some T cells and may modulate T cell activation and promote IFNγ and IL-17 production [43,44]. BAFF also induces dendritic cells to produce IL-12 and supports both the survival of monocytes and their differentiation into activated macrophages [45]. In a mouse model of arthritis, synovial dendritic cells transduced with an siRNA that silences BAFF remained in an immature state and failed to produce the IL-6 required for the differentiation of T helper type 17 cells [43]. Activated monocytes and dendritic cells primarily express intracellular TACI, but cell surface TACI expression may be induced during inflammatory conditions [45]. Thus BAFF appears to have a pro-inflammatory role; it helps DCs and monocytes to activate and recruit immune cells and it directly enhances the pro-inflammatory activity of T cells. These functions are important because BAFF is often expressed in target organs in autoimmune diseases and may therefore contribute to amplification of inflammation in these sites.

BAFF and APRIL inhibitors in lupus mouse models

Several strategies have been developed to block BAFF and APRIL *in vivo*. Selective inhibition of BAFF is achieved with soluble BAFF-R or with antibodies to BAFF; in contrast, soluble TACI blocks both BAFF and APRIL [3,46]. Because the phenotype of APRIL transgenic and knockout mice is not dramatic there has been little interest in developing APRIL specific drugs for the treatment of autoimmunity.

Extensive studies of the mechanism of action of BAFF and APRIL blockade have been performed in murine models of lupus. In several lupus strains, BAFF-R-Ig and TACI-Ig delay the onset of lupus nephritis and prolong survival with similar efficacy [3,47], indicating that BAFF blockade alone is sufficient to mediate therapeutic effects. Due to the different ways that the inhibitors were given, a direct comparison between strains is difficult. However, several studies provide evidence supporting the role of genetic background in determining how long and how effectively lupus-prone mice are protected by BAFF/APRIL inhibition. For example, a single injection of an adenovirus expressing BAFF-R-Ig resulted in protein expression for 6-8 weeks but a thirty week delay in time to death in NZB/W F1 mice [3]. In comparison, when NZM2410 mice were treated with the same dose of virus, survival was prolonged for much longer [47]. Moreover, while both BAFF-R-Ig and TACI-Ig reversed established nephritis in NZM 2410 mice, remission induction in NZB/W F1 mice required the addition of a second agent [3,47].

BAFF/APRIL inhibition does not block the production or the renal deposition of autoantibodies in most mouse lupus strains and even complete deficiency of BAFF does not completely ablate autoantibody production or prevent the eventual development of renal pathology [48]. Plasma cells that produce autoantibodies may arise from germinal centers, extrafollicular foci, or reactivated memory B cells; the source of autoantibodies is variable among mouse strains. In MRL/lpr mice most autoantibody producing plasma cells derive from extrafollicular foci and their survival is largely dependent on TACI and BCMA. TACI-Ig treatment therefore prevents the appearance of both IgM and IgG anti-dsDNA antibodies and renal deposition of immune complexes in this strain [49]. BAFF-R deficiency is not sufficient to inhibit autoantibody formation or prevent lupus nephritis in MRL/lpr mice [50], consistent with the absence of a role for BAFF-R in plasma cell survival.

BAFF/APRIL inhibitors do not prevent the spontaneous formation of germinal centers in the spleens of NZB/W, NZM2410 or NZW/BXSB lupus mice [47,51,52], despite the diminished size of B cell follicles caused by B cell depletion. Autoreactive B cells undergo somatic hypermutation and affinity maturation in these germinal centers, and therefore acquire the ability to bind the kidney antigens. In NZB/W and NZW/BXSB mice, TACI-Ig depletes mainly short-lived IgM producing plasma cells with little effect on long-lived plasma cells that produce IgG autoantibodies [3]. These data suggest that, depending on the predominant autoantibody source in an individual strain, BAFF/APRIL blockade may or may not affect autoantibody production.

The contribution of autoreactive memory B cells to the overall pool of autoantibodies either in mice or humans with SLE is not yet fully understood. While BAFF does not support the survival or reactivation of class switched memory B cells under physiologic circumstances [34], it is possible, given the ability of BAFF to collaborate with inflammatory cytokines to promote plasma cell development from memory cells that BAFF inhibition may prevent memory B cells from differentiating into plasma cells in SLE.

Since the therapeutic effects of BAFF/APRIL inhibitors are not necessarily achieved by preventing the formation of autoantibodies in murine models or in humans, questions remain about the precise mechanism of action of these drugs. B cell depletion decreases the non-secretory functions of B cells and leads to diminished numbers of activated T cells and dendritic cells. As a result, the overall load of circulating pro-inflammatory mediators is reduced, preventing the activation of endothelial cells and local inflammation in the kidneys in response to immune complex deposition [3,47,52]. Nevertheless in NZB/W mice the therapeutic effect of BAFF inhibition appears to be more robust than that of B cell depletion, an effect also observed in humans.

It is possible therefore that BAFF inhibition has direct effects on cells other than B cells. Notably, in Lyn deficient mice BAFF blockade directly inhibits the activation of T cells and decreases the secretion of IFNγ [44]. BAFF/APRIL blockade may also exert protection through direct inhibition of renal cell activation and local kidney inflammation. Regardless of the precise mechanism, BAFF/APRIL inhibition or even BAFF deficiency does not seem to prevent disease onset completely. Furthermore, it is clear that while BAFF blockade consistently demonstrates the same effects on spleen cell populations and autoantibodies in most murine models of SLE, the clinical effect of BAFF blockade on SLE nephritis varies in the different murine models and with disease stage [3,47]. This may reflect the presence of other mediators that collaborate with autoantibodies in the effector phase of renal inflammation or with BAFF in supporting plasma cell survival. Thus, in addition to genetic factors, environmental exposures may influence the therapeutic response to BAFF inhibition. Given the heterogeneity of human SLE patients, it will not be surprising to find that certain subsets of patients respond better to BAFF/APRIL inhibition than others.

BAFF and APRIL inhibition for human disease

Despite considerable immunologic differences between rodents and humans the results of the human studies are consistent with those of the mouse studies. In humans, BAFF blockade preferentially depletes naïve and transitional B cells but has little effect on class switched memory B cells and long-lived plasma cells [53]. Selective BAFF blockade has less effect on serum Ig levels than does blockade of both BAFF and APRIL, and both agents preferentially decrease serum levels of IgM. Clinical trials of belimumab and atacicept have been performed in several autoimmune diseases [4-6,37,54,55].

Because increased serum BAFF levels are found in rheumatoid arthritis (RA) patients and both BAFF and APRIL are detected in rheumatoid synovium [56], the first clinical trials of BAFF inhibitors were performed in RA. The effect of both belimumab and atacicept was modest in this disease [5], a disappointing result given the murine studies showing that local BAFF inhibition alters dendritic and T cell function within the joint [43] and the robust effect of anti-CD20 antibodies in RA patients; these studies did not translate into the desired therapeutic effect of BAFF inhibition in human RA. A recent phase II clinical trial of a different anti-BAFF antibody that targets both membrane and soluble BAFF has shown efficacy in RA and further trials are in progress (M Genovese, abstract 1923). Should this drug be effective in larger trials it will be important to understand whether the targeting of membrane BAFF is responsible for the differences in efficacy between this drug and belimumab or atacicept.

Even more disappointing have been preliminary results of a clinical trial of atacicept in multiple sclerosis (MS). Based on the emerging view that B cells are important in the pathogenesis of MS, and the findings that BAFF is expressed within ectopic lymphoid follicles in the meninges and by astrocytes that are closely associated with BAFF-R expressing cells [57], BAFF/APRIL inhibitors were found to ameliorate early experimental allergic encephalomyelitis in mice [58]. Despite these promising findings, a phase II trial of TACI-Ig in human MS was stopped because of disease worsening (www.clinicaltrials.gov). These results, like those in RA, stand in contrast to the long-lasting clinical benefit conferred by B cell depletion with anti-CD20 antibodies.

Given the pathogenic role of BAFF in murine SLE and the urgent need for new drugs that can ameliorate this disease in humans there has been a large effort directed at studying the efficacy of BAFF inhibitors in human SLE. In an initial phase II trial of belimumab, the primary endpoints of the trial were not met, however there appeared to be some improvement in treated patients at 56 and 76 weeks when a post-hoc analysis using a composite disease outcome measure was performed [37]. Given the slow kinetics of B cell depletion mediated by BAFF inhibition in humans, a decrease in clinical activity of SLE might be expected over a long time period. Two subsequent phase III studies were therefore designed to be of long duration (up to 76 weeks) and the composite disease outcome measure was used as the primary outcome. In addition other interventions were allowed during the first 6 months of treatment before the maximal clinical effect of BAFF inhibition was expected. Using this design, both trials met their primary endpoint at 52 weeks, with a modest benefit over standard of care therapy and improvements in secondary outcomes including the frequency of severe flares and ability to decrease steroid dose. Belimumab did not however demonstrate a significant benefit over standard of care therapy at 76 weeks although several secondary outcomes were still achieved (R.F. van Vollenhoven, abstract OP0068 presented at EULAR Congress, Rome, 2010 and S. Navarra, abstract SAT0204 presented at EULAR Congress, Rome, 2010).

Depletion of B cells in belimumab treated patients occurred predominantly in the naive and transitional populations, becoming maximal 6-8 months after starting therapy. In contrast, depletion of plasma cells and memory cells took more than a year and occurred nearly exclusively in the IgM populations with little effect on the IgG populations. Total serum IgG levels decreased by only 10% and autoantibody titers decreased to a modest degree, consistent with the dependence of plasma cells on both BAFF and APRIL. In a few patients however autoantibody titers disappeared entirely, reflecting some heterogeneity in the immunologic response [37,53]. It is not yet clear whether belimumab alters B cell selection, a question that is important to answer in order to determine potential benefits of long-term belimumab use. The effect of belimumab on T cells and monocytes has not yet been studied.

Similar immunologic effects were observed in phase I study of atacicept in SLE patients [4,6] with a more profound effect on serum immunoglobulin levels, especially IgM and IgA. Nevertheless, serum IgG levels decreased by only 20% and titers of antibodies to recall antigens were not affected, suggesting that long-lived plasma cells in most humans are not dependent solely on BAFF and APRIL for their survival. However, a combination trial of atacicept with mycophenolic acid in patients with SLE nephritis was halted due to hypogammaglobulinemeia and increased infection risk, indicating that plasma cell survival may be compromised when T cell-derived cytokines are also depleted. Further studies of atacicept in SLE are ongoing. Whether there will be some individuals whose plasma cells are totally dependent on BAFF and APRIL remains to be determined.

Conclusions

Inhibition of BAFF or BAFF and APRIL may be a suitable therapeutic approach for SLE The murine studies in sum show that blockade of BAFF delays disease onset in most models of SLE. However, there is considerable strain and environment dependent variation with respect to efficacy, especially in the later stages of disease, with some strains requiring a second synergistic agent to reverse ongoing inflammatory disease. Furthermore, there is considerable heterogeneity in BAFF or APRIL-dependence of plasma cells in different models; this may depend on the presence or absence of other cytokines able to support plasma cell survival and the nature of the microenvironment in which these cells reside. BAFF blockade also decreases the inflammatory response to immune complex deposition in target organs by mechanisms that remain to be fully elucidated. These studies are consistent with the heterogeneity observed thus far in the response of human SLE patients to BAFF inhibition. As belimumab moves towards the formal approval process, questions remain about which diseases will respond to BAFF inhibition, how to identify drug responders, the appropriate duration of treatment and the use of concomitant immunosuppressive therapies. As new members of the BAFF/APRIL class progress through clinical trials we should learn the relative benefits of blocking APRIL or the BAFF membrane or splice variant forms. Finally, it is important to learn why there are disease specific differences in therapeutic efficacy between BAFF/APRIL inhibition and B cell depletion with anti-CD20 antibodies, in particular their relative effects on IL-10 producing B cells (B regs), on non-B cells and the consequences of the high levels of BAFF that accompany B cell depletion and skew the reconstituting B cell repertoire toward autoimmunity

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Abbreviations

SLE	Systemic Lupus Erythematosus
APRIL	A proliferation inducing ligand
BAFF	B cell activating factor belonging to the TNF family (also known as BLyS. B lymphocyte stimulator)
TACI	Transmembrane activator and calcium modulator ligand interactor
BCMA	B cell maturation antigen
BAFF-R	BAFF receptor
HSPG	heparan sulphate proteoglycan
TLR	toll like receptor
IFN	interferon
BCR	B-cell receptor
RA	rheumatoid arthritis
MS	multiple sclerosis

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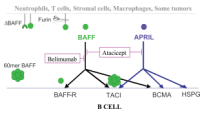

Figure 1.

The interaction of BAFF/APRIL with their receptors and the targets of belimumab and atacicept. Soluble BAFF shed from the cell surface following protease cleavage, binds to BAFF-R, TACI, or BCMA, whereas APRIL only binds to TACI or BCMA. BAFF trimers bind to BAFF-R and BAFF multimers bind to TACI. APRIL is multimerized on the cell surface by heparan sulfate proteoglycan (HSPG). ΔBAFF, a splice variant of BAFF, forms heterotrimers with full length BAFF thus limiting its availability. Belimumab (anti-BAFF) inhibits the interaction of soluble BAFF with its receptors, leaving APRIL functions intact whereas atacicept (TACI-Ig) blocks the binding of both BAFF and APRIL to their receptors.

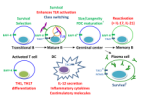

Figure 2.

Effects of BAFF/APRIL on various immune cells in SLE. BAFF supports the survival of transitional and mature B cells and BAFF levels regulate the stringency of selection of naïve B cells. Autoreactive B cells internalize nucleic acids and upregulate TACI as a result of TLR ligation; BAFF/APRIL may therefore preferentially enhance the survival and class switching of these cells and further induce TLR upregulation. BAFF/APRIL also support the long-term survival of plasma cells. In addition, BAFF amplifies the ability of inflammatory cytokines to reactivate memory B cells and induces their differentiation to plasma cells. Finally, BAFF may be involved in survival, activation, differentiation, or cytokine production of T cells and BAFF/APRIL may influence the function of DCs, monocytes, or intrinsic renal cells, contributing directly to local inflammation in the target organs. Functions of BAFF are shown in green. Functions of both BAFF and APRIL are shown in blue. Functions of BAFF or APRIL that occur during inflammation are shown in red.

* the interaction of TACI with APRIL

[#] TACI is responsible for maintaining Type II T independent immune responses

[†] Probably mediated via the interaction of BAFF with TACI

[‡] IgM plasma cells are more BAFF/APRIL dependent than IgG plasma cells