Chapter 8

The Roles of the TNF-Family Member B-Cell Activation Factor Belonging to the TNF-Family (BAFF) in Autoimmunity

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Additional information is available at the end of the chapter

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Abstract

The tumor necrosis factor superfamily (TNFSF) member and cytokine known as B-cell activation factor belonging to the TNF-family (BAFF) has been identified as one of the key factors in the selection and survival of B cells. Overexpression of BAFF in mice leads to autoimmunity, whereas BAFF-deficient mice lack mature B cells. Although under normal concentrations of BAFF, non–self-reactive B cells survived and autoreactive B cells were deleted, a higher concentration of BAFF contributed to the survival of autoreactive B cells and elevated autoantibody production. Lupus-prone mice have increased serum levels of BAFF during the onset and progression of disease. The serum BAFF levels are elevated in patients with autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome and ANCA-associated vasculitis, and showed positive correlations with autoantibodies. Based on the development of autoimmune disorders in animal models of BAFF overexpression and the elevated levels of serum BAFF in patients with autoimmune diseases, it appears that BAFF may be associated with autoimmune processes and that BAFF may be a potential biomarker for disease activity in autoimmune diseases. BAFF may also be important as a therapeutic target in those diseases and several BAFF-neutralizing agents are currently undergoing clinical trials.

Keywords: B-cell activation factor belonging to the TNF-family, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, systemic vasculitis, belimumab, atacicept

1. Introduction

B cells are associated with autoimmune diseases (in functions such as the production of pathogenic autoantibodies) and with multiple pathogenic functions such as autoantigen

uptake and transport, autoantigen presentation to T cells, the production of humoral factors and migration to sites of inflammation. As one of the key factors in the selection and survival of B cells, a closely related cytokine of the tumor necrosis factor (TNF) superfamily (TNFSF) was identified, i.e., the B-cell activation factor belonging to the TNF-family (BAFF). Here we review the physiology of BAFF and its receptors, the roles of BAFF and the effects of BAFF blockade in autoimmune diseases.

2. The basic characteristics of BAFF

2.1. BAFF and its receptors

BAFF (also known as B-lymphocyte stimulator) is a member of the TNF superfamily 13B (TNFSF13B) of proteins that regulate immune responses [1, 2]. The gene for BAFF is located on human chromosome 13q34 and on mouse chromosome 8 [3]. BAFF exists in two forms, a membrane-bound form and a soluble form. Membrane-bound BAFF can be released from cells via proteolytic cleavage from a furin protease site by metalloproteases and released in a soluble form [4].

Soluble BAFF mainly exists in the form of homotrimers. An *in vitro* study showed that 20 BAFF trimers may associate to form a multimeric BAFF 60-mer (which exhibits a virus-like structure) at a neutral or alkaline pH; at an acidic pH, the BAFF 60-mer dissociates into BAFF trimers [5]. However, whether soluble BAFF does or does not form BAFF 60-mer *in vivo* is a controversial question [6]. BAFF is expressed on the surface of many cell types, including antigen-presenting cells (B cells, monocytes, macrophages, dendritic cells) [7, 8], neutrophils [9] and activated T cells [10]. BAFF mRNA has also been detected in bone marrow-derived stromal cells, astrocytes and fibroblast-like synoviocytes in response to proinflammatory cytokines [11].

Soluble BAFF binds to three receptors that are present on several immune cell types—i.e., BAFF-receptor (BAFF-R; also known as BR3 and TNF-receptor superfamily 13C), transmembrane activator and calcium modulator and cyclophilin-ligand interactor (TACI; also known as TNF-receptor superfamily 13B) and B-cell maturation antigen (BCMA; also known as TNF-receptor superfamily 17)—at various times during their differentiation [1]. BCMA is expressed on transitional type 1 (T1) cells [12] and on plasma cells [13, 14], whereas TACI and BAFF-R are expressed on innate immune B cells (marginal zone B cells and transitional type 2 [T2] B cells) and mature B cells [12].

A proliferation-inducing ligand (APRIL), which is a member of the TNFSF (TNFSF13A), was identified as the homologous molecule of BAFF [15]. The gene for APRIL is located on human chromosome 17p13.1 and on mouse chromosome 11 [16]. Similar to soluble BAFF, soluble APRIL exists mainly in the form of homotrimers. APRIL differs from BAFF in that APRIL is not present on the cell surface. APRIL is processed by the Golgi apparatus, which involves cleavage at the furin protease site and the resulting soluble APRIL is released from the cell [17]. Although APRIL trimers are unable to form a multimeric 60-mer, APRIL trimers bind to heparan sulfate proteoglycans (HSPGs) and the binding of multiple APRIL to HSPGs enhances

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local APRIL signaling [18]. Moreover, HSPGs provide a platform for APRIL multimerization, which promotes the occurrence of APRIL multimerization [19].

Thus, the BAFF system involves two ligands (BAFF and APRIL) and three receptors (BAFF-R, TACI and BCMA) and the ligands take three forms (membrane-bound, soluble homotrimers and the multimeric form) (**Figure 1**) [1]. However, APRIL binds to TACI and BCMA but not to BAFF-R [20]. Membrane-bound BAFF and the multimeric BAFF 60-mer binds to BAFF-R, TACI and BCMA, whereas the soluble homotrimers BAFF binds to only BAFF-R [20, 21]. BAFF-R is expressed on resting, marginal zone and germinal center B cells and TACI is expressed on mature B cells and plasma cells [20, 21]. BCMA was identified prior to BAFF-R as a receptor for BAFF [22, 23], but its expression is restricted to germinal center B cells, memory B cells and plasma cells [24–26]. BCMA is a high-affinity receptor for APRIL, whereas in humans BCMA binds BAFF with low affinity.

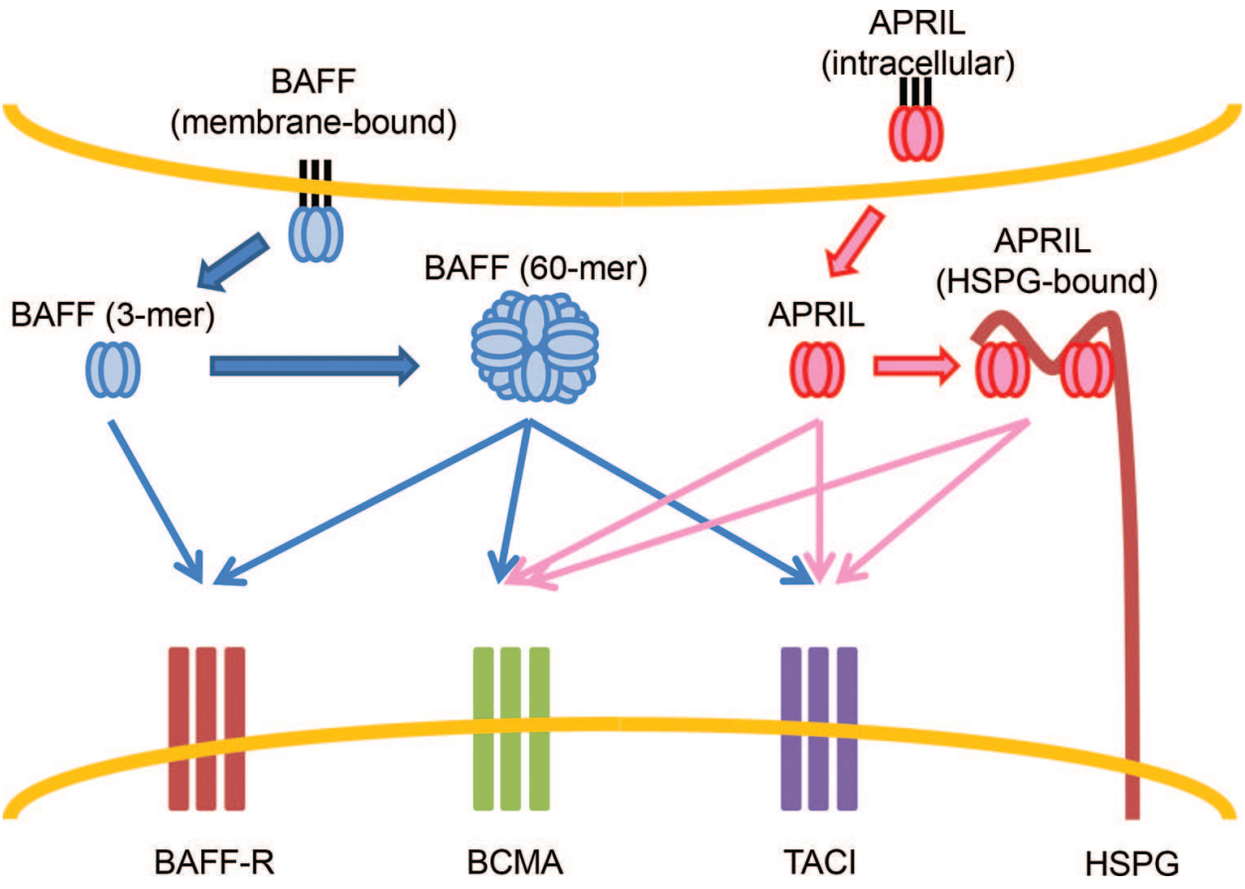

Figure 1. The BAFF system involves two ligands (BAFF and APRIL) and three receptors (BAFF-R, TACI and BCMA) and the ligands take three forms (membrane-bound, soluble homotrimers and the multimeric form).

2.2. Functions of BAFF

The B cells differentiate from hematopoietic stem cells to pro-B cells, pre-B cells, immature B cells, T1 B cells, T2 B cells, mature B cells, activated B cells, memory B cells and plasma cells sequentially and the interaction of BAFF with BAFF-R is essential for the survival of T2 B

cell [1, 22, 27]. Increased competition for BAFF results in a deletion of autoreactive B cells, whereas decreased competition for BAFF in the context of B-cell lymphopenia or increased levels of circulating BAFF results in a relaxation of the B-cell selection and a release of more autoreactive naïve B cells. BAFF-R is upregulated by B-cell receptor (BCR) ligation on mature B cells [28] and is expressed on resting memory B cells [14].

However, it is clear that the survival and reactivation of B-cell memory is BAFF-independent. BAFF-R mediates most BAFF-dependent functions in the naïve B-cell population [29], whereas BCMA is needed for the optimal generation of long-lived plasma cells [30]. Survival of plasma cells expressing TACI and/or BCMA depends on either BAFF or APRIL secreted by dendritic cells and monocyte/macrophages in the lymph node or bone marrow [31]. In contrast, peritoneal B1 cells do not require BAFF or APRIL for their survival [1].

BAFF also plays an important role in immunoglobulin production and class switching. T cell-independent type II responses require the interaction of multimeric BAFF 60-mer or membrane-bound BAFF with TACI [32–34]. TACI-deficient mice have decreased serum IgM and decreased IgM responses to T-independent antigens, but they have increased B-cell numbers and develop an autoimmune phenotype [35]. BAFF induces the CD40-independent immunoglobulin-class switching through the interaction of B cells and the dendritic cells; human dendritic cells upregulate BAFF and APRIL induced immunoglobulin-class switch from Cμ to Cγ and/or Cα genes in B cells in the presence of IL-10 and TGF-β and in the presence of IL-4, BAFF and APRIL-induced immunoglobulin-class switch from Cμ to Cε [35]. IgG responses are much less BAFF-dependent and class-switching to IgA appears to be dependent upon the interaction of APRIL, multimerized by proteoglycans, with TACI [36, 37].

BAFF is an essential component of the innate-immune response and is induced in myeloid dendritic cells by type I interferons (IFNs) [38]. BAFF upregulates toll-like receptor (TLR) expression, promotes B-cell survival and promotes immunoglobulin class-switching and plasma cell differentiation together with interleukin (IL-6) [39, 40]. The activation of TLR-9 in B cells by oligodeoxynucleotides containing CpG motifs upregulates the expression of TACI and increases BCR-mediated signaling [39, 41]. In contrast, the activation of TLR-4 in B cells by lipopolysaccharides upregulates BAFF-R and induces the activated B cells to become susceptible to Fas/CD95-mediated apoptosis [42].

2.3. BAFF-R signaling

Membrane proximal signaling by BAFF-R has been attributed to the TNFR-associated factor (TRAF) molecules, which bind directly or via adapter molecules to intracellular domains of TNFRSF members [43, 44]. Although only TRAF3 binds BAFF-R directly [45, 46], signaling occurs via the concerted actions of TRAF2 and TRAF3, which negatively regulate the receptor [43]. Thus, mice lacking TRAF2 or TRAF3 exhibit a phenotype consistent with BAFF transgenic mice and can persist *in vitro* in the absence of survival factors as well as *in vivo* in the absence of BAFF [47–50]. On the other hand, the inactivation of TRAF3 also allowed for

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the formation and maintenance of the marginal zone B-cell compartment [49, 50], indicating that both BAFF-dependent survival and differentiation signals are dependent upon TRAF2/TRAF3. TRAF2 and TRAF3 are recruited, leading to the release of NF-κB-inducing kinase (NIK), which phosphorylates IKK1, leading to p100 processing to p52 and the activation of NF-κB (**Figure 2**).

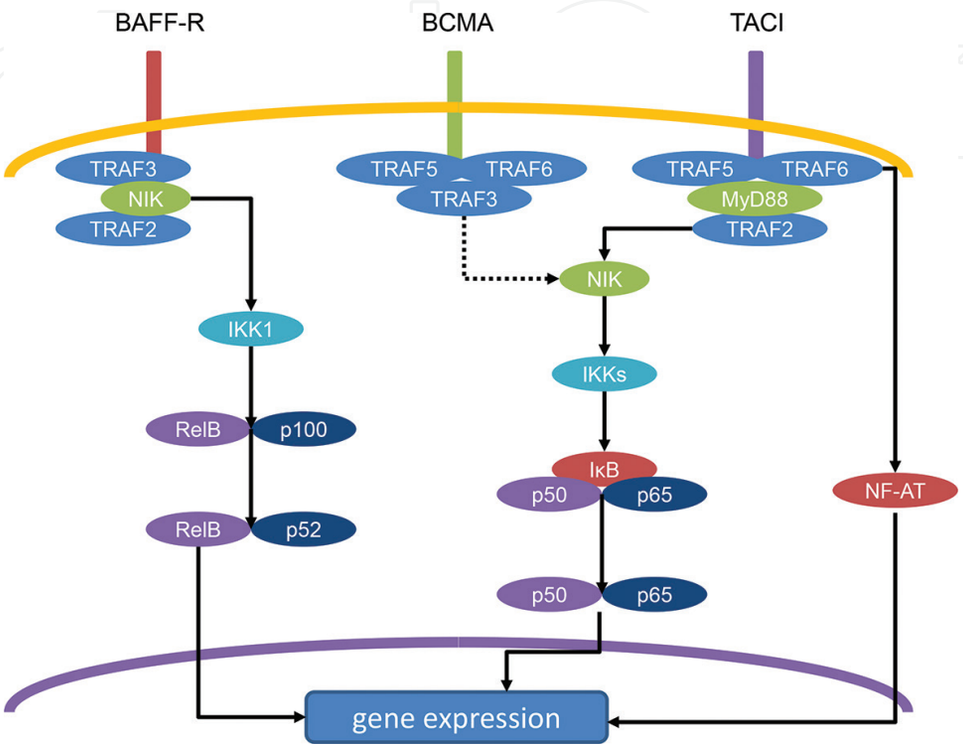

Figure 2. Signaling of three BAFF receptors (BAFF-R, TACI and BCMA).

TACI intracellular domain interacted with TRAF2, TRAF5 and TRAF6 and these interactions induce NF-κB and JNK activations [51, 52]. On the other hand, in immunoglobulin class-switch signaling, TACI can activate NF-κB in the myeloid differentiation primary response protein 88 (MyD88)/the interleukin-1 receptor-associated kinase 4 (IRAK4)-dependent manner similar to TLR signaling [53]. MyD88 and TRAF2 bind to the same region of TACI and acts cooperatively to activate NF-κB [53]. BCMA, BAFF-R and CD40 do not share the ability to bind MyD88.

BCMA-deficient mice have normal B-cell development and the life span of mutant B lymphocytes is comparable to that of wild-type B cells [54]. Moreover, the humoral immune responses of BCMA-deficient mice to T-cell-independent and -dependent antigens were also intact [54]. However, in BCMA-deficient mice, the reduced number of long-lived IgG-producing bone marrow plasma cells was demonstrated compared with wild-type mice [13] and BCMA may be the receptor on plasma cells critical for plasma cell survival. An overexpression of BCMA in human embryonic kidney 293 cells activated canonical NF-κB signaling and coimmunoprecipitation studies indicated that BCMA could interact with NIK and the

IKK complex [55, 56]. Consistently, the survival of long-lived plasma cells does not require BAFF but is dependent upon APRIL [18, 57]. Thus, much remains to be known regarding BCMA signaling by APRIL/BAFF in terminally differentiated plasma cells.

3. BAFF in autoimmune diseases

3.1. Animal models

3.1.1. BAFF-deficient or transgenic models

Mice deficient in BAFF lack T2 B cells, mature marginal zone and follicular B cells and have significantly reduced spleen weights, whereas B-cell differentiation and/or proliferation in bone marrow, T1 B cells and other hematopoietic cell lineages appear normal [22, 58]. BAFF-deficient mice have a reduction in the total serum immunoglobulin level and show diminished T cell-independent and T cell-dependent antibody responses [22, 58]. On the other hand, the phenotypes of BAFF-, BCMA-, TACI- and BAFF-R-deficient mice clearly indicate that the BAFF survival signal in transitional and mature B cells is mediated by BAFF-R in mice and not through BCMA and TACI [22, 34, 54, 58, 59].

Mice transgenic (Tg) for BAFF have vastly increased numbers of mature B and effector T cells and they develop autoimmune-like manifestations such as the presence of high levels of rheumatoid factors (RFs), circulating immune complexes, anti-DNA autoantibodies and immunoglobulin deposition in the kidneys, closely mimicking human systemic lupus erythematosus (SLE) and Sjögren's syndrome (SjS) [47, 60, 61]. These Tg mice showed also severe enlargement of the spleen, lymph nodes and Peyer's patches because of an increased number of B220 cells and hypergammaglobulinemia contributed by elevations of serum IgM, IgG, IgA and IgE was observed [61].

Older BAFF-Tg mice demonstrate characteristics of SjS, such as enlarged salivary glands due to inflammation and leukocytic infiltrates and reduced saliva production as a consequence of acinar cell destruction [62]. BAFF induced the survival of a subset of splenic immature B cells, referred to as T2 B cells [63]. BAFF treatment allowed T2 B cells to survive and differentiate into mature B cells in response to signals through the B-cell receptor (BCR) [63]. The T2 and the marginal zone B-cell compartments were particularly enlarged in BAFF Tg mice [63].

Immature transitional B cells are targets for negative selection, a feature thought to promote self-tolerance [63]. Although BAFF overexpression did not affect the development of self-reactive B cells normally deleted in the bone marrow or during the early stages of peripheral development, BAFF overexpression rescued from deletion of selfreactive B cells, which normally deleted around the late T2 stage of peripheral development [64]. Moreover, self-reactive B cells normally selectively deleted from the marginal zone repopulated this compartment by BAFF overexpression [64]. This partial subversion of B-cell self-tolerance is likely to underlie the autoimmunity associated with BAFF overexpression (**Figure 3**).

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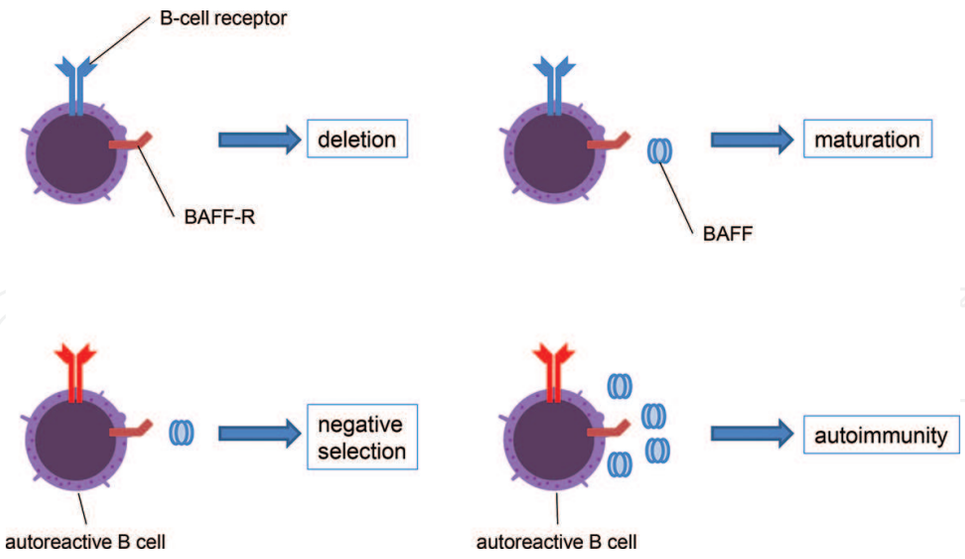

Figure 3. The associations B-cell maturation or B-cell self-tolerance and BAFF expressions.

3.1.2. Animal models of autoimmune diseases

In two murine models of human SLE, MRL/Mp-lpr/lpr and NZB/W F1 mice, there are increased serum levels of BAFF that seem to correlate with autoimmune kidney damage [60]. In NZB/W F1 mice, treatment with soluble TACI-Ig fusion protein inhibits the development of proteinuria and prolongs survival of these mice [60]. In BXSB murine lupus model, treatment with soluble fusion protein consisting of human BAFF-R and human mutant IgG4 Fc resulted in significant reduction in peripheral and splenic B-cells and in proteinuria [65]. In SLE-prone NZM 2328 mice deficient in BAFF, serum autoantibody levels and glomerular IgG and C3 depositions were significantly reduced compared with wild-type NZM 2328 mice [66] and those clinical and pathological responses were more resistant to disease-promoting properties of IFN-α [67].

3.2. Human autoimmune diseases

Similar to BAFF-R-deficient mice, humans with the BAFF-R gene deletion have severe B-cell lymphopenia. B cells are arrested at the transitional B-cell stage and this condition presents with adult-onset antibody-deficiency syndrome [68]. Humans with this condition have diminished numbers of mature B cells, e.g., follicular, marginal zone and memory B cells and their T-independent immune responses are severely impaired.

In relation to the possible role of BAFF in autoimmunity, patients with autoimmune diseases such as SLE, RA, SjS and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) have all been shown to have elevated levels of BAFF.

3.2.1. Systemic lupus erythematosus

The BAFF levels of 110 plasma samples and 40 serum samples from 150 SLE patients were found to be elevated compared to the samples from 40 normal controls [69]. In that study, the

SLE patients with high levels of BAFF exhibited significantly higher levels of antidouble-strand-DNA antibody in each of the IgG, IgM and IgA classes compared to the SLE patients with low levels of BAFF and the normal controls [69]. In a study of serum BAFF levels in 185 patients with various systemic immune-based rheumatic diseases (including 95 with SLE, 67 with RA, 23 with other diseases), serum BAFF levels were elevated in 21% of the 185 patients and those levels in the SLE patients correlated with the antidouble-strand-DNA antibody titers [70].

In a longitudinal study of serum BAFF levels in 68 SLE patients, the serum BAFF levels were persistently or intermittently elevated in 50% of the patients and the blood BAFF mRNA levels were also elevated in 61% of the patients [71]. In SLE patients with elevated serum BAFF levels, treatments with high-dose corticosteroids led to a marked reduction of the serum BAFF levels [71]. Regarding the association of serum BAFF levels with disease activity, those levels were correlated with not only antidouble-strand-DNA antibody titers but also the safety of estrogens in lupus erythematosus: National Assessment (SELENA) version of the systemic lupus erythematosus disease activity index (SLEDAI) score in 245 patients with SLE [72].

Of the peripheral blood mononuclear cells (PBMCs) from normal controls, only CD14+ cells (monocytes) expressed surface BAFF and this expression tended to be very modest, whereas the level of BAFF expression was frequently increased in PBMCs from SLE patients and some CD14− cells as well as CD14+ cells were present [71]. In another SLE cohort of 60 patients, the peripheral blood leukocyte levels of BAFF mRNA were correlated with the serum BAFF protein levels and the BAFF mRNA levels were more closely associated with serum immunoglobulin levels and SLEDAI scores than were the serum BAFF protein levels [73]. In 75 SLE patients, elevated serum BAFF and elevated PBMC BAFF mRNA levels in active SLE patients were observed compared with those in stable SLE patients and controls and those levels in active SLE patients with proteinuria were higher than those in active SLE patients without proteinuria [74].

BAFF-R expressions on CD27−CD38low (resting naïve) and CD27+CD38low (resting memory) B cells were equivalent between SLE patients and controls, but those expressions on CD38+ (germinal center) B cells and CD27+CD38++ (plasmablast) cells were reduced compared to controls [75]. The occupancy of BAFF-R on B cells from SLE patients would render them less responsive to exogenous BAFF [75]. BAFF-R expressions on CD19+IgD+CD27−, CD19+IgD+CD27+ and CD19+IgD−CD27+ B cells in SLE patients were reduced compared to controls [76]. Decreased BAFF-R expressions on CD19+ B cells were more obvious in SLE patients with nephritis, whereas the expression of TACI on CD19+ B cells in lupus nephritis was upregulated [76].

BAFF-R expressions on CD19+ B cells were correlated with negative SLEDAI scores [76], but TACI expression in CD19+ B cells was positively correlated positively with the SLEDAI score [77]. The expression of BAFF-R on CD19+ cells (B cells) in active SLE patients was downregulated compared to those in stable SLE patients and controls and the expression of BAFF-R on CD19+ cells was negatively correlated with serum BAFF levels and BAFF mRNA levels in PBMCs [74]. Thus, elevated BAFF in serum and PBMCs and a reduced expression of BAFF-R and overexpression of TACI on B cells were demonstrated in SLE.

3.2.2. Rheumatoid arthritis

It was demonstrated that serum BAFF levels in 67 rheumatoid arthritis (RA) patients were higher than those in 48 normal controls and elevated serum BAFF levels were correlated with serum IgG levels and RF titers in 42 RA patients [70]. The serum BAFF levels in 53 patients with RA were higher than those in 39 healthy controls, but lower than those in 41 patients with Sjögren's syndrome [62]. In 129 patients with autoimmune diseases including 28 RA patients, elevated serum levels of BAFF correlated with RF titers [78]. Elevated serum BAFF levels were observed in an early RA stage: serum BAFF levels were higher in 48 early RA patients (disease duration <1 year) compared to 48 patients with rheumatic disease other than RA or 50 healthy controls, but not 49 patients with longstanding RA (disease duration >1 year) [79]. In 48 early-RA patients, the serum BAFF levels correlated with IgG-, IgA- and IgM-RF titers and anti-CCP antibody levels [79]. Thus, serum BAFF levels were elevated in RA patients and those levels were associated with autoantibodies, including RF titers.

Synovial fluid levels of BAFF in RA patients were more elevated than the serum BAFF levels in the same patients and the synovial fluid and serum BAFF levels were correlated with each other [80]. The synovial fluid levels of BAFF in RA patients were also correlated with monocyte, lymphocyte, neutrophil and total nucleated cell counts [80]. In mononuclear cells extracted from the synovium of RA patients, BAFF and BAFF mRNA were expressed on B cells, T cells and monocytes [81]. In that study, BAFF was not expressed on the surface of fibroblast-like synoviocytes (FLSs) extracted from the synovium of RA patients, but BAFF mRNA was detected in FLSs [81]. There was no difference in BAFF mRNA of FLSs from the synovial tissue of RA patients compared with those from patients with osteoarthritis and the normal controls, but the BAFF mRNA of those cells was enhanced by IFN-γ or TNF-α [82]. In cocultures of peripheral B cells with FLSs from synovial tissue of RA patients, the expression of RAG genes—which could induce a revision of the B-cell receptor genes, resulting in autoreactivity—was induced in peripheral B cells by BAFF and IL-6 [83]. Moreover, a BAFF-dependent class switch recombination was demonstrated in the coculture of peripheral B cells with FLSs from synovial tissue of RA patients [84]. These findings suggested that the overexpression of BAFF may be associated with autoimmunity at sites of inflammation in RA.

There was no difference in the BAFF-R expression on peripheral naïve B (CD19+CD27−) and memory B (CD19+CD27+) cells among RA patients before treatment, RA patients during remission and normal controls, but the BAFF-R expression on both types of B cells in RA patients at relapse was significantly lower than that in the RA patients before treatment and the normal controls [85]. Although the BAFF-R expressions on PBMCs and B cells were reduced, BAFF-R in synovial tissues from RA patients was highly expressed [86].

However, in another study, the BAFF-R expression on peripheral B cells increased with disease progression (very early, early and established RA) and the TACI expression on peripheral B cells increased in all stages of RA patients [87]. Thus, elevated BAFF in serum and synovial tissue of RA was demonstrated, but the BAFF-R expression varied.

3.2.3. Sjögren's syndrome

It was demonstrated that serum BAFF levels in 41 patients with SjS were higher than those in 53 SLE patients, 53 RA patients and 39 healthy controls [62]. In the investigation of both serum BAFF and APRIL, in a comparison with six healthy donors the serum levels of both BAFF and APRIL in 29 SjS patients were elevated, but compared with SjS patients without anti-SSA antibody, only the serum APRIL levels in the SjS patients with anti-SSA antibody were elevated [88].

Although the serum BAFF levels failed to correlate with anti-SSA antibody, anti- SSB antibody or RF in those studies, several other studies demonstrated that the serum BAFF levels correlated with autoantibodies [78, 89, 90]. In 49 patients with SjS, elevated serum levels of BAFF were demonstrated compared to those in 47 healthy controls and there was a strong correlation between the serum BAFF levels and anti-SSA antibodies and RF levels [89]. In 129 patients with autoimmune diseases including 58 SjS patients, elevated serum levels of BAFF in the SjS group were correlated with anti-SSA antibody [78]. In an investigation of 127 SjS patients, elevated serum levels of BAFF in SjS correlated with anti-SSA and anti-SSB antibodies [90]. Serum BAFF levels in SjS patients with hypergammaglobulinemia were also elevated compared to those of patients with normal IgG levels [91].

The serum BAFF levels in SjS patients with the formation of ectopic germinal centers were elevated compared to those of patients without ectopic germinal centers [92]. BAFF mRNA expression and production in circulating monocytes and T cells from SjS patients by IFN-α stimulation were higher than those from normal controls [93]. The expression of BAFF and its mRNA were also demonstrated in T cells infiltrating labial salivary glands of biopsy specimens from SjS patients [94]. In salivary glands, BAFF expressions were also observed in IFN-stimulated salivary gland epithelial cells [95] and infiltrating B cells [96]. These findings suggested that BAFF may be associated with the immunopathogenesis of SjS.

Unstimulated peripheral monocytes from 13 SjS patients produced higher amounts of BAFF and IL-6 compared to those of 12 healthy donors [97]. In that study, the expressions of BAFF-R and transcription factors regulating IL-6 in monocytes from SjS patients were also elevated. Thus, BAFF may also be associated with monocyte activation.

Although elevated BAFF in serum and salivary glands of SjS patients were demonstrated, the BAFF-R expression varied. The expression of BAFF-R on peripheral B cells in 20 SjS patients was decreased compared to that in 15 controls and there was no difference in BAFF-R mRNA levels of B cells between SjS patients and controls [98]. On the other hand, in a study of BAFF-R expression in the salivary glands, the expression of BAFF-R on B cells was observed, but the expressions of TACI and BCMA were not [96].

Serum BAFF levels differed among SjS patients with and without lymphoproliferative disorders (lymphoma or prelymphomatous manifestations): higher levels of serum BAFF in 42 SjS patients with lymphoproliferative disorders were demonstrated compared to those in 34 SjS patients without these disorders [99]. A higher frequency of the minor T allele of the rs9514828 BAFF polymorphism in the high-risk SjS group for lymphoma was demonstrated [100]. Moreover, in SjS patients with younger-age onset (at <40 years old), the generalized odds ratio

for the development of mucosa-associated tissue lymphoma was 6.1 in the presence of the BAFF-R His159Tyr mutation [101]. These findings suggested that BAFF may also associated with an increased risk of progression to lymphoma.

3.2.4. ANCA-associated vasculitis

Several studies of serum BAFF levels in AAV patients have been reported. It was demonstrated that the serum BAFF levels in 46 granulomatosis with polyangiitis (GPA) patients were significantly elevated compared to those of 62 healthy controls [102]. Elevated serum BAFF levels were observed in untreated GPA patients, but that level in corticosteroid-treated GPA patients was approximately the same as in the healthy controls. Similarly, elevated serum BAFF levels were observed in 87 patients with proteinase-3 (PR3)-AAV compared to the levels of 31 healthy controls, but the BAFF levels in relapsed patients did not differ from those in patients without relapse [103]. In a study of 22 GPA patients, serum BAFF levels were correlated independently and inversely with PR3-ANCA levels, but did not correlate with clinical parameters, i.e., the Birmingham vasculitis activity score (BVAS), the vasculitis damage index (VDI) and the disease extent index (DEI) and with the serum C-reactive protein (CRP) level [104]. Thus, serum BAFF levels in GPA were elevated, but the association between the BAFF level and the PR3-ANCA titer was not established.

Among three types of AAV (41 patients with GPA, 16 patients with microscopic polyangiitis [MPA] and four patients with eosinophilic GPA), elevated serum levels of BAFF were observed only in GPA patients [105]. However, several studies demonstrated that serum BAFF levels were elevated in MPA patients [106, 107]. In myeloperoxidase (MPO)-AAV, the serum BAFF levels in 23 active vasculitis patients were higher than those in 24 inactive vasculitis patients, 13 inactive vasculitis patients with infectious complication and 20 controls [106]. Moreover, there were significant positive correlations between the serum levels of BAFF and the BVAS results, the serum CRP levels and the MPO-ANCA titers.

Similar to those findings, in a study of 121 patients with MPO-AAV (100 of whom had MPA, 18 had GPA and three had renal-limited vasculitis), the serum BAFF levels were significantly elevated in both the patients with active disease and those in remission compared to healthy controls, although the patients with active disease still had significantly higher levels than those in remission. In that study, the serum BAFF levels correlated well with the BVAS results and the erythrocyte sedimentation rate (ESR), but they did not correlate with the MPO-ANCA titer [107]. Thus, serum BAFF levels in MPA were elevated, but the association between the BAFF level and the MPO-ANCA titer was not clear.

In an *in vitro* study of BAFF expression and release in stimulated neutrophils, treatment with PR3-ANCA-IgG significantly increased BAFF expression in neutrophils compared to the expression in untreated and normal IgG-treated cells [108]. Supernatants from PR3-ANCA-IgG-stimulated neutrophils were shown to contain increased levels of BAFF compared to those from untreated and normal IgG-treated neutrophils [108]. Supernatants from neutrophils treated with PR3-ANCA but not normal IgG induced an increase in the cell viability of a B-cell line [108]. In a study of the *in vitro* IgG production in stimulated PBMCs from GPA patients, IL-21 enhanced the production of IgG, whereas stimulation with BAFF alone did

not result in increased IgG production [109]. However, the combination of BAFF and IL-21 increased the IgG production more than IL-21 alone [109].

The combination of BAFF and IL-21 induced a significant enhancement in PR3-ANCA production in PBMCs isolated from ANCA-positive patients in comparison with ANCA-negative patients [109]. The stimulatory effect on IgG and PR3-ANCA production by BAFF and IL-21 was further enhanced by the addition of exogenous factors (oligodeoxynucleotides containing CpG motifs) [110]. These findings suggested that elevated BAFF may be associated with ANCA production by autoreactive B-cell survival.

Decreased expression of BAFF-R on circulating B cells and decreased expression of TACI on circulating memory B cells were demonstrated [110]. In another study, there was no difference in soluble TACI levels among active MPO-AAV patients, inactive MPO-AAV patients and controls [111]. On the other hand, in a histological study of biopsy samples from eight patients with GPA, activated B cells in nasal mucosa were located alongside PR3-expressing cells and BAFF-producing cells and BAFF-R-expressing B cells were also identified in the nasal mucosa [112]. The expression of BCMA on plasma cells, lymphocytic and fibroblast-like cells in sinonasal biopsy specimens from GPA patients were elevated, compared to those from nonautoimmune inflammatory rhinosinusitis [113]. In this study, TACI-expressed cells displaying plasma-cell-like morphology were present in sinonasal biopsy specimens from only GPA patients [112]. Although elevated serum BAFF in AAV was demonstrated by several investigations, further studies of BAFF-R in AAV were needed.

3.2.5. Other autoimmune diseases

In addition to systemic autoimmune diseases, the serum BAFF level is also elevated in organ-specific autoimmune diseases. Antiglomerular basement membrane (GBM) disease is an autoimmune disease characterized by the presence of anti-GBM autoantibodies. The most common clinical features include rapidly progressive glomerulonephritis and/or alveolar hemorrhage (goodpasture disease). The serum levels of BAFF in patients with anti-GBM disease were significantly higher than those in normal controls [114]. Although serum BAFF levels were not correlated with anti-GBM antibodies titers, those levels were associated with the percentage of glomeruli with crescents. Elevated serum BAFF levels were also demonstrated in patients with Graves' disease [115], autoimmune pancreatitis [116], myasthenia gravis [117], idiopathic thrombocytopenic purpura [118] and multiple sclerosis [119].

4. Anti-BAFF agents in autoimmune diseases

Several biologic drugs have recently been developed in an attempt to block the BAFF-BAFF receptors pathway: belimumab, atacicept, tabalumab and blisibimod. Belimumab is a human monoclonal antibody that antagonizes the effect of BAFF by binding to the free form of the cytokine [120]. Atacicept is a TACI-Fc fusion protein that binds to and blocks the receptor for both BAFF and APRIL [121]. It acts both in homotrimers and heterotrimers and results in diminished plasma cell survival and antibody production in mice and humans [121].

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Tabalumab and blisibimod both block the two biologically active forms of BAFF; tabalumab is a human monoclonal antibody and blisibimod is a fusion polypeptide protein [122].

Animal models have shown that BAFF antagonists substantially delay the onset of disease in SLE-prone NZB/W mice [59, 123, 124] and prevent collagen-induced arthritis in DBA1 mice [125]. Clinical trials of anti-BAFF agents have also been performed as described below.

4.1. Belimumab

Belimumab was the first anti-BAFF drug to be evaluated in RA patients. In a phase II study, patients fulfilling the American College of Rheumatology (ACR) criteria for RA for equal to or greater than 1 year who had at least moderate disease activity while undergoing therapy with a stable disease-modifying antirheumatic drug (DMARD) and failed equal to or greater than 1 DMARD were randomly assigned to placebo or belimumab 1, 4, or 10 mg/kg treatment, administered intravenously (IV) on days 1, 14 and 28 and then every 4 weeks for 24 weeks (n = 283) [126]. The American College of Rheumatology 20% improvement criteria (ACR20) responder rates after 24 weeks of treatment with placebo and belimumab 1, 4 and 10 mg/kg, defined as the primary endpoint, were 15.9, 34.7, 25.4 and 28.2%, respectively, indicating relatively low efficacy of belimumab in this RA cohort [126]. This study was followed by an optional 24-week extension (n = 237) in which all patients received belimumab and patients received belimumab had an ACR20 response of 41% at 48 weeks [126].

Three major trials of belimumab in SLE have been reported. In a phase II study, patients with a SELENA-SLEDAI score equal to or greater than 4 (n = 449) were randomly assigned to belimumab (1, 4, or 10 mg/kg) or placebo in a 52-week trial [127]. There was no significant reduction in SELENA-SLEDAI scores from baseline; 19.5% in the combined belimumab group versus 17.2% in the placebo group. The median time to first SLE flare was 67 days in the combined belimumab group versus 83 days in the placebo group.

The BLISS-52 trial included 865 SLE patients with moderate-to-severe disease (SELENA-SLEDAI score equal to or greater than 6) and positive ANA and/or anti-dsDNA who were randomized to receive IV belimumab 1 mg/kg (n = 289) or 10 mg/kg (n = 290) or placebo (n = 288) [128]. Fifty-eight percent of the autoantibody-positive SLE patients in the 10 mg/kg belimumab group showed an improved systemic lupus erythematosus responder index (SRI) at week 52 versus 44% in the placebo group. In the patients treated with belimumab 1 mg/kg, 51% had an improved SRI value at week 52, which was also a significantly better response than placebo group. In addition, belimumab was shown to be well tolerated; it reduced disease activity and improved serologic activity, prevented flares and reduced corticosteroid use.

The BLISS-76 study was conducted in 819 patients who were randomized to receive IV belimumab 1 mg/kg (n = 271) or 10 mg/kg (n = 273) or placebo (n = 275) for 72 weeks [129]. The primary efficacy endpoint in this study was the same as the BLISS-52 trial and 43.2% of the SLE patients in the 10 mg/kg belimumab group were SRI responders versus 33.5% in the placebo group at 52 weeks, although at 76 weeks there was no significant difference in response rate among three treatment groups (response rates at week 76 were 32.4, 39.1 and 38.5% with placebo, 1 mg/kg belimumab and 10 mg/kg belimumab, respectively).

In a phase II open-label clinical trial of belimumab for SjS, a total of 30 SjS patients were treated with 10 mg/kg belimumab in weeks 0, 2 and 4 and every 4 weeks until week 24. The mean dryness, fatigue and pain visual analogue scale (VAS) values changed from 7.8 to 6.2 ($p = 0.0021$), 6.9 to 6.0 ($p = 0.0606$) and 4.6 to 4.7, respectively. However, there was no significant change in the salivary flow or the Schirmer's test score [130].

4.2. Atacicept

Similar to the outcome with belimumab, a Phase Ib study or 73 RA patients treated with six escalating doses of atacicept demonstrated good local and systemic tolerability to the drug. Patients received atacicept or placebo as single doses (70, 210, or 630 mg) or as repeated doses given at 2-week intervals (three doses of 70 mg, three doses of 210 mg, or seven doses of 420 mg), followed by 10 weeks of trial assessments, with a follow-up assessment at 3 months after the final dose [131]. Treatment-related decreases in immunoglobulin (particularly IgM) and RF levels were evident and a clear decrease in anticitrullinated protein antibodies was observed in the cohort that received seven doses of 420 mg [131]. However, further studies with atacicept did not demonstrate significant efficacy in RA patients with inadequate response to methotrexate (MTX) [132] or tumor necrosis factor antagonists [133].

In a 52-week Phase II/III study of atacicept in SLE, at screening (day 14), patients were started on a regimen of high-dose corticosteroid (the lesser of 0.8 mg/kg/day or 60 mg/day prednisone) and mycophenolate mofetil (MMF; 0.5 g twice daily, increased to a maximum of 1.5 g twice daily). From Day 1, atacicept (150 mg, subcutaneously, twice weekly for 4 weeks, then 150 mg weekly for a planned 48 weeks) was initiated with MMF along with a tapered dose of corticosteroid [134]. However, the trial was terminated after the enrollment of six patients, due to an unexpected decline in serum IgG and the occurrence of serious infections; three of four atacicept-treated patients developed serious infections in association with low IgG levels [134].

In another 52-week Phase II/III study, patients with moderate-to-severe SLE were randomized to atacicept 75 mg or atacicept 150 mg administered subcutaneously or placebo twice-weekly for 4 weeks, then weekly for 48 weeks [135]. Although there was no difference in flare rates or time to first flare between the atacicept 75 mg and placebo groups, flare rates in patients treated with atacicept 150 mg were decreased compared with placebo (flare rate 43 and 60%, respectively; odds ratio [OR]: 0.49) and atacicept 150 mg was associated with a significant delay in time to first flare (hazard ratio [HR]: 0.56) [135]. Both atacicept doses were associated with reductions in total immunoglobulin levels and anti-dsDNA antibodies and with increases in C3 and C4 levels [135]. However, enrollment in the atacicept 150 mg arm was discontinued prematurely due to two deaths.

4.3. Tabalumab

In a Phase II study of tabalumab in RA, patients who were naïve to biologic therapy received infusions of tabalumab (30, 60, or 160 mg) or placebo at weeks 0, 3 and 6 in combination with MTX and were evaluated for 24 weeks [136]. The percentages of patients achieving an ACR20 response at week 16 in the 30-mg, 60-mg and 160-mg groups were significantly greater than the percentage of patients achieving an ACR20 response in the placebo group (57.6, 67.6, 51.5 and 29.4%, respectively) [136]. In a Phase II dose-ranging study [137], RA patients on stable

MTX (n = 158) were randomized to receive 1, 3, 10, 30, 60, or 120 mg tabalumab or placebo subcutaneously every 4 weeks for 24 weeks. The observed ACR50 response rate was significantly higher with only the 120 mg dose versus placebo at week 12 (33.3 vs. 11.1%) and week 20 (33.3 vs. 8.3%), but not at week 24. The ACR20 response rate was significantly higher with 120 mg versus placebo at week 12 (66.7 vs. 33.3%) and week 24. No other dose was significantly different from placebo at any time point for ACR20, except 60 mg at week 4 (38.5 vs. 11.1%).

However, in a 52-week Phase III study that enrolled 1041 patients with moderate-to-severe RA despite ongoing MTX, the evaluation of subcutaneous tabalumab 120 mg every 4 weeks or 90 mg every 2 weeks versus placebo, there were no significant differences in ACR20 responses at week 24 among treatment groups [138]. Another Phase III trial (called the FLEX-O study) enrolled 1004 patients who received subcutaneous 120 mg tabalumab every 4 weeks, 90 mg tabalumab every 2 weeks, or placebo over 24 weeks with a loading dose double the planned dose (240 mg, 180 mg, or placebo) at baseline. No differences in the ACR20 response rates were observed at week 24 (34.4, 33.5 and 31.5%) or any other measures of efficacy across the treatment groups [139].

In another Phase III study, 456 patients with active RA were evaluated after 24-week treatment with subcutaneous tabalumab (120 mg every 4 weeks or 90 mg every 2 weeks) versus placebo, with loading doses (240 or 180 mg) at week 0. There was no significant difference in week 24 ACR20 responses among the three groups (17.6, 24.3 and 20.0%) per a nonresponder imputation analysis [140].

In a study of tabalumab in SLE, a total of 2288 SLE patients were randomized (n = 1164 in ILLUMINATE-1 and n = 1124 in ILLUMINATE-2) to receive tabalumab or placebo [141, 142]. In the ILLUMINATE-1 study, 1164 patients with moderate-to-severe SLE (SELENA-SLEDAI score equal to or greater than 6 at baseline) received subcutaneous injections of tabalumab or placebo, starting with a loading dose (240 mg) at week 0 and followed by 120 mg every 2 weeks (n = 387), 120 mg every 4 weeks (n = 389), or placebo (n = 388). Similar proportions of patients in each group achieved an SRI-5 response at week 52 (31.8, 35.2 and 29.3% placebo), but an SRI-5 response was achieved with 120 mg every 4 weeks (37.0 vs. 29.8% placebo), but not 120 mg every 2 weeks (34.1%) and significant reductions in anti-dsDNA antibodies, increases in C3 and C4 and reductions in total B cells and immunoglobulins were observed with tabalumab [141].

In the ILLUMINATE-2 study, 1124 patients with moderate-to-severe SLE (SELENA-SLEDAI score equal to or greater than 6 at baseline) received subcutaneous injections of tabalumab or placebo, starting with a loading dose (240 mg) at week 0 and followed by 120 mg every 2 weeks (n = 372), 120 mg every 4 weeks (n = 376), or placebo (n = 376). An SRI-5 response at week 52 was achieved in the 120-mg every 2 weeks regimen (38.4 vs. 27.7%, placebo), but not with the less-frequent 120 mg every 4 weeks regimen (34.8%) [142]. Anti-dsDNA levels decreased in both tabalumab groups as early as week 4 and continued to decrease, remaining well below baseline levels through week 52.

4.4. Blisibimod

In the phase Ia study of single-dose blisibimod, SLE patients with mild disease that was stable/inactive at baseline enrolled into one of seven dose cohorts: 0.1, 0.3, 1.0, or 3.0 mg/kg subcutaneous or 1.0, 3.0, or 6.0 mg/kg intravenous blisibimod and subjects were sequentially enrolled

into one of four dose cohorts: 0.3, 1.0, or 3.0 mg/kg subcutaneous or 6.0 mg/kg intravenous in phase Ib study of multiple-dose blisibimod [143]. Blisibimod changed the constituency of the B-cell pool and single and multiple doses of blisibimod exhibited approximate dose-proportional pharmacokinetics across the dose range 1.0–6.0 mg/kg. The PEARL-SC study was a 24-week treatment, Phase IIb randomized trial of 547 SLE patients with moderate-to-severe disease (SELENA-SLEDAI) score equal to or greater than 6 at baseline) who received placebo or blisibimod at one of three dose levels in an evaluation of the efficacy and safety of blisibimod [144]. Although the SRI-5 response rates were not significantly improved in the pooled blisibimod groups compared with placebo, they were higher in the patients randomized to the highest dose of blisibimod (200 mg once-weekly) compared to the pooled placebo group at week 20. In the patients with protein:creatine ratios of 1–6 at baseline, significant reductions in proteinuria were observed with blisibimod. Significant changes in anti-dsDNA antibodies, complement C3 and C4 and reductions in B cells were observed with blisibimod treatment.

5. Conclusion

Based on the results of studies of autoimmune disorders in animal models of BAFF overexpression and the elevated levels of serum BAFF observed in patients with autoimmune diseases, it appears that BAFF may be associated with autoimmune processes and that BAFF may be a potential biomarker for disease activity in autoimmune diseases. BAFF may also be important as a therapeutic target in those diseases and several BAFF-neutralizing agents are currently undergoing clinical trials.

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