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# BAFF System in Rheumatoid Arthritis: from Pathobiology to Therapeutic Targets

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Additional information is available at the end of the chapter

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## Abstract

Recent advances in understanding the multifaceted pathobiology of rheumatoid arthritis have highlighted the pivotal role and continuing crosstalk between activated immune cells, pro-inflammatory cytokines, and matrix-degrading mediators, promoting chronic inflammation as well as irreversible tissue damage within an autoimmune background. B cells are widely recognized as leading players in immune-mediated pathology based on their ability to produce not only different patterns of autoantibodies and driving cytokine synthesis but also as independent antigen-presenting cells and by modulating the specific activation of T cells. Overwhelming evidence emphasized the role of BAFF, a B-cell-activating factor, and BAFF receptors (TACI, BCMA, BAFF-R) in promoting B-cell homeostasis, proliferation, and survival under normal and autoimmune systemic disorders. We systematically reviewed data from literature focusing on BAFF, its homolog molecule APRIL, and BAFF-binding receptors biology, dysregulation of BAFF/BAFF receptor signaling in autoimmune settings, and current status of targeting BAFF/BAFF receptor pathway for rheumatoid arthritis.

**Keywords:** rheumatoid arthritis, autoimmunity, B-cell-activating factor (BAFF), BAFF-binding receptors, BAFF antagonists

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## 1. Introduction

Rheumatoid arthritis (RA) is a chronic immuno-inflammatory disease characterized by a multifaceted pathobiology, where a complex cytokine and cellular network contribute to excessive and extensive articular and systemic inflammatory events, accompanied by progressive tissue damage [1–4].

B cells are widely recognized as leading players in the mechanisms underlying the pathogenesis of RA based on their ability to produce not only different subsets of autoantibodies but also as independent antigen-presenting cells, cytokine synthesis, and modulators of T-cell activation. Moreover, their differentiation and survival are driven by positive feedback loops induced by cytokines, especially members belonging to the tumor necrosis factor (TNF) family [1–4].

Recent data highlighted the role of signaling crosstalk in B-lymphocytes, particularly of B-cell-activating factor (BAFF) and its receptors in early steps of the disease, advancing clinical development of BAFF antagonists for the treatment of RA [2–5]. Acting as an innate cytokine mediator, BAFF is known to modulate peripheral B- and T-cell homeostasis, promoting specific downstream signaling events through three different types of receptors [2, 4, 5].

Abnormal BAFF/BAFF receptor-signaling pathways were reported in several autoimmune disorders including systemic lupus erythematosus, Sjogren's syndrome, ANCA-associated vasculitis, and RA [2, 4, 5]. Of interest, elevated BAFF levels were detected in synovial fluid, serum, and saliva in very early stages of RA, suggesting its involvement in cell-cell interactions network in the synovial microenvironment, as well as B-cell activation and the development of autoreactive B cells [2–4]. Furthermore, the overexpression of BAFF receptors, as well as disturbed autocrine and paracrine BAFF network, seems to be related to inflammatory events and RA progression [1–6].

Although clinical development of BAFF antagonists as potential therapeutic target for systemic autoimmune conditions is promising, the benefit of specific agents such as belimumab, atacicept, or tabalumab in RA is controversial [2, 4, 6].

We systematically reviewed data from the literature focusing on the biology of BAFF, its homologue molecule APRIL and BAFF-binding receptors, dysregulation of BAFF/BAFF receptor signaling in RA and current status of targeting BAFF/BAFF receptor pathway.

## 2. BAFF and BAFF receptors physiology

### 2.1. BAF and APRIL

BAFF, also known as BLyS (B-lymphocyte stimulator), TALL-1 (TNF and apoptosis ligand-related leukocyte-expressed ligand 1), zTNF4, TNFSF13B (TNF ligand superfamily member 13B) or THANK, is a protein member of the TNF ligand family, critically involved in B-cell survival, maturation, and function [2–6]. As a vital cytokine for peripheral B-cell homeostasis, BAFF is acknowledged as a key regulator for both innate and adaptive immune responses [2–5].

Under normal conditions, BAFF is mainly expressed and secreted by a variety of cells including monocytes, dendritic cells, neutrophils, stromal cells, and activated T cells [2–14] and is typically upregulated by different cytokines, such as TNF- $\alpha$ , IFN- $\gamma$ , and TGF- $\beta$  [2–14].

BAFF is recognized under two isoforms, a biologically active full-length isoform and the alternatively spliced one, 4BAFF, meaning a protein with a small peptide deletion which does

not bind to BAFF receptors, but has the ability to form heterotrimers with the original isoform [2–6]. Additionally, BAFF is expressed as a membrane-binding homotrimer and released as a soluble, biologically active molecule in peripheral blood after cleavage by a dedicated furinprotease [2, 4].

APRIL, a proliferation-inducing ligand known as the homolog molecule of BAFF or TNFSF13 (TNF ligand superfamily member 13), is also a key cytokine for B-cell activation and maturation; APRIL prompts B-cell proliferation, antibody class switching and survival, but is not required for the normal B-cell development [12–14].

Interestingly, BAFF and APRIL exhibit the ability to generate mixed molecules comprising BAFF/APRIL hetero-trimers [2–14] and TWE-PRIL (TNFSF12), an APRIL extracellular domain/TWEAK intracellular domain hybrid molecule [2, 4], as well as  $\Delta$ BAFF, an alternatively spliced form of BAFF [4]. None of these molecules binds to BAFF receptors, but their co-expression with BAFF may have a deleterious impact on receptor signaling [2–14].

## 2.2. BAFF receptors signaling

Three distinct BAFF receptors typically expressed on B cells in different developmental stages are generally recognized: (i) BAFF receptor (BAFF-R, BR-3, TNFRSF13C or TNF receptor superfamily member 13C); (ii) transmembrane activator and calcium modulator ligand interactor (TACI, TNFRSF13B or TNF receptor superfamily member 13B); and (iii) B-cell maturation antigen (BCMA, TNFRSF17 or TNF receptor superfamily member 17) [2–14].

The expression of BAFF-binding receptors becomes evident only during the transitional stages of B-cells, varies according to the B-cell subset and is strictly dependent on various downstream mediators, further differentiation, maturation, and activation level as well [2–14]. Moreover, each receptor triggers its own set of signaling pathways [2, 4].

Thus, BAFF-R is essentially engaged in naïve and memory B-cell populations, with the highest expression in follicular and marginal zone B-lymphocytes, and is upregulated by B-cell receptor on mature B cells and enables most of the BAFF-dependent actions [2–14]. BAFF-R appears to be the most important receptor for mature B-cell survival and homeostasis in peripheral B cells [5].

TACI remains the predominant receptor on marginal zone B cells and short-lived plasma cells, while BCMA is typically expressed by long-lived plasma cells being essential for their optimal generation [2, 4]. The ability of TACI to act as a sink for BAFF, preventing the attachment of BAFF to its BAFF-R, may also reflect mixed regulatory functions on B cells [2, 4, 5, 10–14].

Although BAFF-R/BR3 stands as a specific receptor for both soluble and membrane-bound BAFF, TACI and BCMA can also bind to the homologous proliferation-inducing ligand APRIL [2, 4, 10–14].

Each of the three receptors has a different pattern of expression and mediates distinct functions [2, 4].

2.3. BAFF and BAFF receptors functioning

It is widely accepted that BAFF plays a crucial role in B-cell homeostasis, adjusting their maturation, proliferation, and survival under different backgrounds. BAFF may also indirectly interfere with T-cell functioning, providing several co-stimulatory signals in conjunction with T-cell receptor, mainly related to cellular proliferation and synthesis of mediators [2, 4].

Table 1 summarizes the BAFF/BAFF receptors functions in B and T cells (Table 1) [2–14].

Cell type	Function
B cells	Enhance B-cell and plasma cell survival Co-stimulate B-cell proliferation B-cell maturation Promote B-cell differentiation from transitional type 1 to type 2 cells Immunoglobulin synthesis T-cell-independent and T-cell-dependent antibody response
T cells	Enhance T-cell proliferation Enhance cytokine synthesis
Dendritic cells	Promote immune cell recruiting Promote cytokine synthesis

Source: Adapted from Ref. [2].

Table 1. Overview of main BAFF biological functions in immune cells.

2.3.1. BAFF and B-cell functioning

BAFF and APRIL mediate several important B-cell functions in normal settings, but dysregulated BAFF/BAFF receptors represent a significant event in different autoimmune conditions [2–14].

First, BAFF enhances long-term B-cell survival primarily through NF- $\kappa$ B pathway by upregulating anti-apoptotic Genes, particularly the expression of Bcl-2 gene family members [2–14]. While BAFF and APRIL typically improve the survival of plasmablasts, their role in promoting long-lived plasma cells persistence is still debatable [2, 4]. Moreover, either BAFF or APRIL accounts for the survival of plasma cells expressing TACI and/or BCMA [2, 4, 10–14]. By contrast, memory B cells do not require BAFF nor APRIL for their proliferation and survival [2, 4]. Thus, their survival and reactivation are both BAFF-independent [2, 4, 10–14]. Finally, BAFF-BAFF-R interface seems to be vital for the survival of B2 subpopulation from the transitional type 1 stage, with a minor input from TACI and without feedback from BCMA [2–14].

Second, BAFF enhances signaling through the B-cell receptor (BCR) by upregulating the expression of its co-receptors, namely CD21 and CD19, respectively [2–14]. The relation is bidirectional as BAFF-R expression is upregulated by B-cell receptor on mature B cells [2–14]. Additionally, there is a direct linkage between the intensity of BCR signaling and the extent of BAFF signal, particularly related to the non-classical NF- $\kappa$ B pathway which is operational for BAFF-R [2, 4–14]. Therefore, signaling through BAFF-R is able to promote B-lymphocytes survival in general, and individual late transitional and follicular B-cell survival [2–14].

Third, BAFF upregulates Toll-like receptor (TLR), endorses B-cell survival as well as Ig class switching and plasma cell differentiation [2–14]. The expression of BAFF-bound receptors on B cells, particularly TACI [2–14], is up-regulated via intracellular-activated TLR under the effect of specific immune complexes, with further relevance for augmented BCR-mediated signaling. Activated B cells by TLR-4 overexpress BAFF-R receptor types with subsequent susceptibility to apoptotic signals through Fas molecules [2–14].

Finally, the differentiation of peripheral autoreactive B cells depends on high BAFF levels [2–14].

### *2.3.2. BAFF and T-cell functioning: proliferation and cytokine production*

While recent insights have extensively advanced our knowledge about BAFF/BAFF receptor intervention on B-cell activity in normal microenvironment and autoimmunity, the role of BAFF and APRIL in T-cell co-stimulation is still controversial [2, 4–14].

Classically, BAFF indirectly enhances T-cell proliferation [8] and arbitrates cytokine production, particularly during inflammation. Hence, the expansion of T-cell population may occur as a consequence of primary B-cell expansion/proliferation rather than a result of direct intervention of BAFF cytokine. Of interest, APRIL itself appears to mediate T-cell overflow [2–14]. T-cell-dependent immunoglobulin (Ig) responses strictly vary according to Ig subtype; IgM responses require BAFF intervention, whereas IgG responses are usually BAFF-independent [2–15]. Also, the intervention of BAFF receptors on T-cell function is debatable; while TACI might refashion T-cell functions, BAFF-R charge is unclear [2–14].

### *2.3.3. BAFF and dendritic cells functioning*

It is increasingly recognized that BAFF influences dendritic cells to be actively involved in many physiologic as well as pathologic processes. Dendritic cells not only overexpress BAFF under different mediators (e.g., type I interferons) but also express BAFF receptors, predominantly TACI required for cellular proliferation and function [2–14]. The interaction between BAFF and dendritic cells stimulates immune cell trafficking and recruitment to inflammatory sites, and delivery of different cytokines and chemokines, mainly IL-1 and IL-6 [2–14].

## **3. BAFF and BAFF receptors in rheumatoid arthritis**

Dysregulated BAFF/BAFF receptor signaling is clearly a trigger for autoimmunity in particular settings as is the case of systemic lupus erythematosus and RA [1, 2, 4, 5, 15–24]. To better understand the relevance of BAFF/BAFF receptor system in the complex pathobiology of RA with direct involvement in both early stages and disease progression, we emphasized several aspects regarding cell networking and BAFF influences, BAFF levels, and BAFF receptor expression in RA [2, 4, 15–24].

### **3.1. BAFF and BAFF receptor influences on cell networking in rheumatoid arthritis**

We already mentioned the effects of BAFF in B- and T-cell biological homeostasis in general, and we further provide information on how BAFF and APRIL influence immune cells and resident synovial cells in RA [2, 4, 15–24].



RA is thought to be the result of an interplay between multiple cells and their products (cytokines and mediators), from both innate and adaptive immunity that lead to systemic inflammatory and tissue-damaging events [1–4].

Persistent immune cell trafficking into the inflamed joints typically focuses on B- and T-lymphocytes, with special polarization for TCD4<sup>+</sup> subpopulation, neutrophils, macrophages, and dendritic cells, which actively infiltrate the RA synovium and orchestrate inflammation and cartilage damage [1–4]. At least three different histological subtypes of immune infiltrates are actually recognized within the RA synovitis, meaning diffuse, nodular infiltrates, and lymphoid aggregates with germinal centers [2–4].

Excess of pro-inflammatory cytokines (mainly TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-15, IL-17, and IL-23) and other inflammatory mediators (prostaglandin E2, reactive oxygen Species, nitric oxide) together with tissue-degrading enzymes (matrix metalloproteinases and other enzymes synthesized by activated neutrophils) are essential performers, maintaining local cellular network in RA joints [1–3].

As innate cytokines, BAFF and APRIL are potentially involved in the dysregulated immuno-inflammatory synovial microenvironment, affecting both autocrine and paracrine feedback [1–6]. In addition, BAFF and APRIL are involved in an amplification loop which is locally activated by inflammation: B- and T-lymphocytes, together with plasmacytoid and myeloid dendritic cells, are interconnected through a continuing crosstalk [1–4]. Thus, B cells migrated to the inflamed tissues and activated produce pro-inflammatory and destructive cytokines and chemokines, but also exert their potent effector function by presenting self-antigens to and activating T cells [2–4]. Moreover, immune complexes as a result of aberrant functioning of B cells induce the activation of different subtypes of dendritic cells within the IFN direct supervision and further enhance B- and T-participation [4].

### *3.1.1. Neutrophils, macrophages, dendritic cells, and B-lymphocyte loop in rheumatoid arthritis*

It is clear that activated neutrophils, macrophages, as well as dendritic cells represent fundamental sources of BAFF in the inflamed RA joints; however, these cells may have variable importance in different RA stages, with neutrophils releasing BAFF in early RA, while macrophages in established disease [1–4, 14–24].

Abundant BAFF levels further support a positive feedback from B-lymphocytes, the BAFF/BAFF-R signaling being an important stimulator of B-cell proliferation, survival, and activation, with subsequent dysregulated B-cell functioning, with synthesis of various cytokines, and autoantibodies [1–4, 14–24].

Neutrophils incoming in the inflamed synovial joint is able to produce high levels of soluble BAFF under the direct action of TNF- $\alpha$  and local G-CSF [1–4]. Additionally, through BAFF-R reverse signaling [2–4], macrophages are able to enhance MMP-9 and other matrix-degrading mediators [2–4]. Dendritic cells express BAFF molecule in early RA stages and turn into mature dendritic cells, mediating B-cell proliferation [2–4] with subsequent increase in antigen presentation, antibody production, immune complex formation, and cytokine secretion [1–4].

### *3.1.2. Neutrophils, macrophages, dendritic cells, and T-lymphocytes loop in rheumatoid*

BAFF may also interfere with T cells-dendritic cells interaction. BAFF is obviously involved in T helper 1 (Th1)-related immune responses [1–4, 14–24] and facilitates significant in situ CD4<sup>+</sup> T-cell proliferation and Th1 as well as Th17 polarization [1–4]. Interestingly, pro-inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$  are involved in upregulation of BAFF expression on various activated cells in the synovial microenvironment (macrophages, dendritic cells, neutrophils) enhancing Th17 polarization and subsequent synthesis of IL-17 cytokine [1–4].

### *3.1.3. Fibroblast-like macrophages, B- and T-cell loop in rheumatoid arthritis*

Fibroblast-like macrophages are known to constitutively express BAFF in patients with RA, and BAFF expression is significantly upregulated under TNF- $\alpha$  and IFN- $\gamma$  stimulation [2, 4]. Activated fibroblast-like macrophages are further able to secrete IL-6 and CXCL12, as well as adhesion molecules (VCAM-1) influencing the survival of mature B cells and synovial trafficking [2, 4]. Recent data suggest that CD4<sup>+</sup> T cells under BAFF activation are able to induce the proliferation of fibroblast-like macrophages, with consequent overexpression of various pro-inflammatory cytokines, particularly TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 [2–4, 14–24].

Overall, various residents as well as recruited cells in rheumatoid synovium are responsible for BAFF synthesis, especially dendritic cells, macrophages and fibroblast-like macrophages, neutrophils, and CD4<sup>+</sup> T cells. Further, BAFF interventions on the effector cell network (dendritic cells, macrophages and fibroblast-like macrophages, neutrophils, TCD4<sup>+</sup> lymphocytes, and B cells) are able to promote by positive feedback their differentiation, proliferation, activation with subsequent cytokine production, and survival [2, 4].

## **3.2. Abnormal BAFF levels in rheumatoid arthritis**

Elevated levels of BAFF are found in several inflammatory diseases (lupus, Sjogren's, RA), and are related to disease activity [2–4]; RA exhibits a positive correlation between BAFF and disease activity, so that BAFF was recommended as a new index of RA activity [2, 4, 14–24].

Interestingly, a recent study designates BAFF as a predictor of RA prognosis and outcomes as serum level of BAFF parallels radiographic progression and higher plasma BAFF correlates with advanced radiographic joint damage [2, 4, 14–24].

Elevated levels of both BAFF and APRIL along with their receptors in patients with RA, particularly in rheumatoid factor (RF) positive, anti-cyclic citrullinated peptide antibodies (ACPA)-positive subtype, active, erosive disease, support their role in the pathobiology of the disease [2, 4, 14–24]. Although abnormal BAFF was typically found in both serum and synovial fluid in RA, significantly higher synovial levels suggest local BAFF production, driving the maturation as well as preserving autoreactive B cells within the inflamed tissue, with subsequent amplification of inflammatory processes and generation of autoantibodies [2, 4, 14–24]. Furthermore, seropositive RA status is clearly associated with higher concentrations of BAFF than seronegative disease [2–4, 14–24], and there is a statistically significant correlation Between RF titer and BAFF level [2–4, 14–24].



Finally, it seems that BAFF levels depend on RA stage, and disease duration as well [2, 4, 14–24]; thereby, patients with very early RA (disease duration less than 6 weeks) have highest BAFF levels, followed by those with established (lasting more than 12 months) and long-standing disease [2, 4, 14–24]. Undifferentiated early arthritis also has lower BAFF levels as compared to very early RA supporting a role for BAFF in the initial steps of disease development [2, 4, 14–24].

However, local BAFF overexpression in RA joints is independent of the histologic subtype of RA synovitis (diffuse, nodular, and germinal center) [2, 4, 14–24]. BAFF also contributes to local B-lymphocyte function and survival, their activation and differentiation with subsequent production of autoantibodies [2, 4, 14–24]. Moreover, BAFF induces an autoreactive B-cell polarization as stressed by several studies in experimental arthritis models [2, 4, 14–24]. Thus, there is an interrelation between BAFF levels and humoral immune response [2, 4, 14–24], particularly RF, ACPA, as well as circulating immune complexes [2, 4, 14–24].

### **3.3. Abnormal expression of BAFF receptors in rheumatoid arthritis**

BAFF receptors are also altered in RA [2, 4, 14–24]. The three receptor subtypes are expressed as follows: TACI-excessive levels are detected during first steps of RA development (early RA), BAFF-R has an obvious increase with disease progression, while BCMA expression has the same pattern as healthy population [2, 4, 14–24]. Furthermore, TACI receptor distribution and expression are typically lower than BAFF-R/BR3, without any relation with the histological subtype of synovitis [2, 4, 14–24]. On the other hand, it seems that only BCMA and its gene expression correlate with different patterns of B- and T-cell distribution among the synovial tissue [2, 4, 14–24]. Thereby, BCMA is significantly enhanced in synovial tissue presenting with follicular lymphocyte aggregation with or without germinal centers formation than in diffuse lymphoid infiltration synovitis [2, 4, 14–24]. Finally, aberrant expression of BCMA in resident synovial cells, Fibroblast-like synoviocytes, was reported in RA [2, 4, 14–24].

## **4. Targeting BAFF and BAFF receptors for rheumatoid arthritis**

Accumulating data on the importance of B cells in various autoimmune diseases have reshaped the therapeutic armamentarium, specifically directed toward B-lymphocytes [2, 4, 25, 26].

While playing a pivotal role in B-cell survival and functioning, BAFF/BAFF receptor system recently emerged as a reasonable target for different autoimmune conditions [2, 4, 25, 26]; furthermore, several BAFF antagonists are already under development exploring the appropriate therapeutic intervention based on BAFF blockade in RA [2, 4, 25, 26].

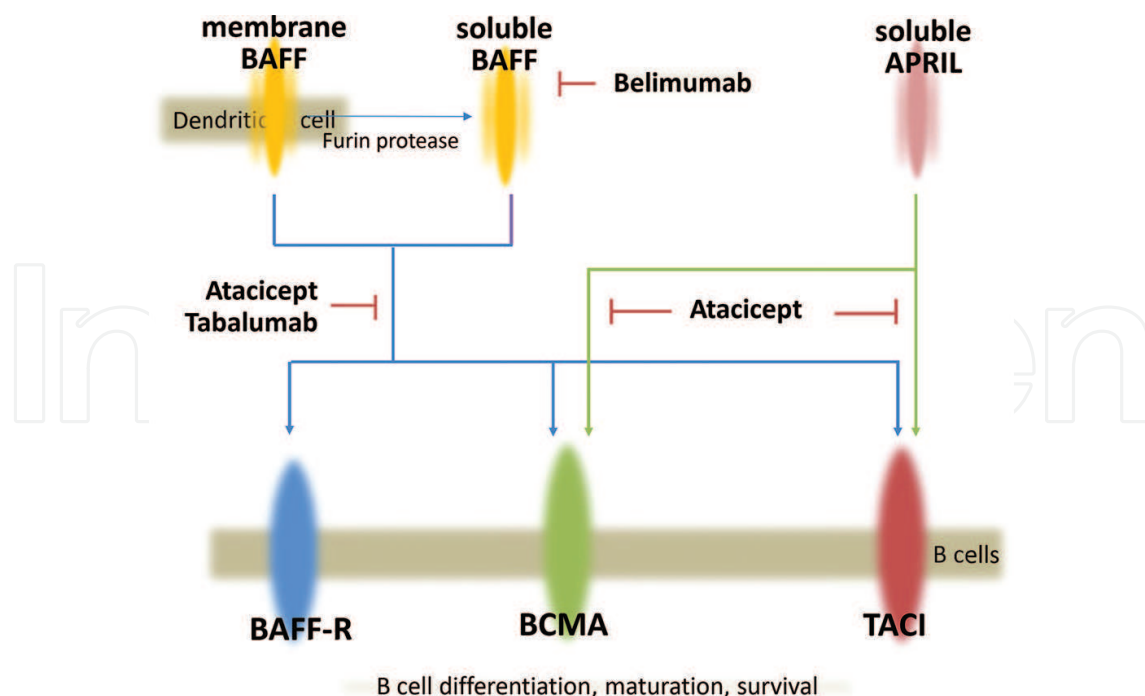
Generally, therapeutic BAFF antagonism accounts not only for direct B-cell depletion and indirect impairment of B-cell-mediated processes such as antigen presentation, cytokine synthesis, and humoral immune response, but may also influence T-cell biology based on co-stimulatory signals [2, 4, 25, 26].

Several mechanisms were proposed to explain potential efficacy of BAFF/BAFF receptors antagonists in autoimmune conditions [2, 4, 25, 26]: (i) substantial B-cell depletion, particularly for bone-marrow-derived B2 subpopulation, known to undergo BAFF-mediated differentiation into follicular cells or marginal zone B cells [2, 4, 25, 26]; (ii) impaired immunoglobulin synthesis, especially in newly emerging B cells, while established memory B cells are spared; decreased transitional B-cell survival along with disturbed B-cell receptor co-signaling may further support altered immunoglobulin repertoire [2, 4, 25, 26]; (iii) indirect effect on other cells belonging to the BAFF amplification loop (T cells, dendritic cells, and macrophages) and their inflammatory mediators promoting decreased antigen presentation, decreased epitope spreading, immune complexes formation, and cytokine synthesis [2, 4, 25, 26]; (iv) selective depletion of plasmablasts expressing different BAFF-binding receptors [2, 4, 25, 26].

At least two classes of BAFF antagonists are currently recognized including (i) BAFF-blockers or monoclonal anti-BAFF antibodies (e.g., belimumab and tabalumab) and (ii) receptor fusion proteins (e.g., atacicept), specifically binding soluble BAFF, membrane BAFF, or APRIL [2, 4, 25, 26].

A simplified view of BAFF/APRIL/BAFF-binding receptor pathway and their targeted therapy in immune mediated is presented (**Figure 1**).

We reviewed the current status of targeting BAFF/BLyS, APRIL and their receptors in RA.



**Figure 1.** BAFF/APRIL/BAFF-binding receptor pathway and targeted therapy. Source: Adapted from Vincent F. et al., Nat Rev Rheum. 2014; Ref. [43].

#### 4.1. Belimumab

Belimumab, the first targeted biological therapy for systemic lupus erythematosus, is a recombinant fully human immunoglobulin G subclass 1 (IgG1k) anti-BAFF monoclonal antibody recently approved for antinuclear antibody-positive lupus, selectively targeting soluble BAFF, but not membrane-bound BAFF or other members of the TNF ligand family. Moreover, belimumab demonstrates inhibitory activity on all three BAFF receptors (TACI, BCMA, BR3) with equivalent potency [2, 4, 26–30].

BAFF overexpression in RA theoretically induces local (synovial) autoreactive B-cell proliferation and survival. Preventing BAFF from binding to B cells is able to impair B-cell-mediated autoimmune response and could be an attractive target for RA patients [2, 4, 26–30].

The efficacy and tolerability of a novel, fully human variant of anti-BLyS monoclonal antibody was further evaluated in patients with active RA non-responsive to standard therapy in different clinical trials [2, 4, 26–30]. While safety data are convincing across all the studies and belimumab seems to be a promising agent for a specific RA population, optimal clinical efficacy needs further evaluation [2, 4, 26–30]. The majority of trials have demonstrated positive outcomes under belimumab BAFF-blockade, meaning significant response rates according to American College of Rheumatology (ACR) improvement  $\geq 20\%$  criteria but not ACR50 or ACR70, specifically for RA patients classified as having high disease activity (disease activity score DAS28  $> 5.1$ ), RF and ACPA-positive status, naïve to other biologics including TNF antagonists, previous methotrexate failure or low baseline BAFF levels [2, 4, 26–30].

#### 4.2. Tabalumab

Tabalumab, formerly LY2127399, is another fully human IgG4 anti-BAFF monoclonal antibody that binds to and neutralizes soluble and membrane-bound BAFF, but not to APRIL [2, 4, 25, 31–35].

Efficacy and safety of tabalumab in active RA despite ongoing methotrexate was assessed in several phase 2 and 3 randomized-controlled studies and their open-label extensions performed on diverse patient populations comprising either bio-naïve or bio-experienced RA with an inadequate response to TNF inhibitors (non-responders or intolerant) [2, 4, 25, 31–35]. Clinical efficacy parameters included standardized measures such as ACR20, ACR50, and ACR70 improvement criteria, DAS28-C-reactive protein (DAS28-CRP), and Health Assessment Questionnaire-Disability Index (HAQ-DI), while total B-cell counts or CD3-CD20 B cells and serum immunoglobulins were used for biological impact [2, 4, 25, 31–35]. Of interest, each one of the four phase 2 clinical trials (identifier NCT00308282, NCT00689728, NCT00785928, and NCT00837811) provided encouraging results under flexible doses of anti-BAFF and a background of stable methotrexate, with meaningful clinical and biological RA improvement as compared to placebo, regardless of prior treatment [2, 4, 25, 31–35]. However, tabalumab received no further validation following two phase 3 randomized, double-blind, placebo-controlled studies aiming to demonstrate drug efficacy and safety in patients with moderate-to-severe RA with inadequate response to one or more TNF inhibitors [25, 30, 34–36]. The interim analyses prompted the withdrawal of tabalumab due to lack of efficacy, not to safety concerns [2, 4, 25, 31–35].

*To summarize*, although tabalumab showed clinical and biological efficacy in phase 2 clinical trials irrespective of prior exposure to synthetic remissive drugs (methotrexate) or biologics, phase 3 trials fail to promote clinical benefit in patients with moderate-to-severe RA with prior inadequate response to TNF antagonists. Despite demonstrating biological improvement as supported by substantial change in B-cell count and decline in serum immunoglobulin levels, it is obvious that targeting the BAFF pathway alone is not a feasible strategy in RA [2, 4, 25, 31–35].

#### 4.3. Atacicept

Atacicept is a recombinant fusion protein between the extracellular domain of one of the BAFF receptors (TACI) and the Fc portion of human IgG1, able to inhibit B-cell maturation, differentiation, and survival, as well as immunoglobulin synthesis by disconnecting B cells from standardized growth and development signals [2, 4, 25, 36–41]. In contrast to BAFF monoclonal antibodies, atacicept not only binds to and neutralizes BAFF but also targets APRIL molecule [2, 4, 25, 36–41] and could be an efficient target for RA treatment by inhibiting activation of TACI-mediated signaling [2, 4, 25, 36–42].

Preclinical and phase 1 clinical studies showed promising results as atacicept was well tolerated, with no increased incidence of infections, and displayed a meaningful biological activity with impaired levels of immunoglobulin, RF and ACPA, and a biphasic response in B-cell count [2, 4, 25, 36–41]. Moreover, atacicept induced substantial clinical improvement, despite the nonlinear pharmacokinetic profile [2, 4, 25, 36–41].

Nevertheless, AUGUST I (Clinical Trials.gov: NCT00430495) and AUGUST II (Clinical Trials.gov: NCT00595413), two phase 2 clinical trials, failed to demonstrate the efficacy of atacicept in moderate-to-severe RA patients. Both studies were specifically designed to assess efficacy, safety, and biological activity of atacicept in RA with an inadequate response to TNF inhibitors (AUGUST I) [2, 4, 25, 36–41] or biologically naive patients suboptimally controlled or intolerant to classic remissive agents (methotrexate) [2, 4, 25, 36–41].

Although the primary efficacy end point (ACR20 response) was not achieved in none of phase 2 studies, atacicept significantly reduced the immunoglobulin (IgM, IgG, and IgA) and rheumatoid factor levels in a dose-dependent manner. The safety profile was acceptable as atacicept did not show an increased susceptibility to infections, although the overall rate of adverse events was somewhat higher than placebo and lupus [2, 4, 25, 36–41].

*To summarize*, despite clinical and biological efficacy expressed in preclinical arthritis models and phase 1 clinical trial, phase 2 studies with atacicept fail to promote clinical benefit in patients with moderate-to-severe RA with inadequate response to either prior TNF antagonists or methotrexate [2, 4, 25, 36–41].

#### 4.4. Other BAFF antagonists (AMG-623 and BR3-Fc)

Other BAFF-blockade agents are under development, targeting different BAFF receptor-binding molecules. A good example is A-623, previously known as AMG-623, a polypeptide fusion protein containing both IgG and the ligand-binding section of the BAFF-R, able to block both membrane and soluble BAFF and, therefore, to impair normal B-cell functioning

[43]. Briobacept or BR3-Fc is another distinct BAFF-blocking molecule acting as a homodimeric fusion glycoprotein including the extracellular ligand-binding portion of BAFF-R and the Fc portion of an IgG. This new drug was typically designed to induce further B-cell apoptosis interfering with BAFF/BAFF-R signaling [2, 4, 43].

## 5. Conclusions

Abnormal BAFF signaling (throughout either overexpression of B-cell-related activation and survival genes, or BAFF receptors) represents an important step in the pathobiology of rheumatoid arthritis, particularly by promoting the development of autoreactive B cells in early disease, but also by supporting disease progression.

Although BAFF/APRIL/BAFF receptors targeting therapy seems to be an attractive option for systemic autoimmune conditions, particularly systemic lupus erythematosus, considerable response heterogeneity and safety concerns are reported in rheumatoid arthritis.

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