

The Role of Glomerular and Serum Expression of Lymphocyte Activating Factors BAFF and APRIL in Patient with Membranous and IgA Nephropathies

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Abstract

Increased activity of B lymphocytes underpins many autoimmune conditions. A key component of the humoral immune response involves the A Proliferation-Inducing Ligand (APRIL) and B-cell-activating factor (BAFF) system. These proteins are responsible for the activation, maturation, and survival of B lymphocytes, playing a pivotal role in autoimmunity. Therefore, targeting the BAFF/APRIL system proves promising for the treatment of various autoimmune diseases. Meticulous research into pathomechanisms of lupus nephritis (LN) has enabled the introduction of biological treatments targeting the BAFF-mediated pathway, significantly improving prognosis. In certain types of glomerulonephritis (GN), increased levels of the BAFF/APRIL system might be associated with higher proteinuria, elevated serum creatinine, but also with specific histopathological features. This indicates that biological therapies currently available could be repurposed for conditions where increased activation of B lymphocytes plays a critical role in the disease's pathophysiology. Understanding the mechanisms underlying autoimmune diseases will facilitate the adaptation of novel drugs for orphan diseases. That is why the use of chimeric antigen receptor T (CAR-T) cells as agents against B-cells receptor (BCR), represents a highly targeted and potentially optimal treatment approach. This study summarizes current knowledge about the role of the BAFF/APRIL system in lymphocyte activation mechanisms, particularly in GN. It also discusses existing biological treatments and explores future directions for drug development based on the CAR-T cell technology.

Keywords

APRIL • autoimmunity • BAFF • glomerulonephritis • IgA nephropathy • membranous nephropathy

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Abbreviations

APRIL, A Proliferation-Inducing Ligand; BAFF = Bly, B-cell-activating factor = B lymphocyte stimulator; BAFF-R, BAFF receptor; BCMA, B-cell maturation antigen; BCR, B-cell receptor; CRR, Complete renal response; eGFR, Estimated glomerular filtration rate; Gd-IgA1, Galactose-deficient IgA1; GN, Glomerulonephritis; IgAN, IgA nephropathy; LN, Lupus nephritis; MN, Membranous nephropathy; RA, Rheumatoid arthritis; RTX, Rituximab; SLE, Systemic lupus erythematosus; SS, Sjögren's syndrome; TACI, Transmembrane activator and calcium-modulator and cyclophilin ligand interactor; Tg, Transgenic; TLR, Toll-like receptor; TNF, Tumor necrosis factor; UPCR, Urine protein-creatinine ratio.

1. The B-Cell-Activating Factor (BAFF), the A Proliferation-Inducing Ligand (APRIL), and the Immune System

Hyperactivation of B lymphocytes is fundamental to many autoimmune diseases, including systemic lupus erythematosus

(SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS). It also plays a key role in the development of various types of glomerulonephritis (GN), such as lupus nephritis (LN), IgA nephropathy (IgAN), and minimal change disease (Oniszcuk et al. 2021; Cai et al. 2023; Petrou et al. 2023). The immune response is divided into innate and adaptive immunity. The innate response is non-specific and includes mechanisms such as phagocytosis by granulocytes and monocytes, as well as the natural killer cell response. In contrast, the adaptive response is specific and generates a reaction tailored to a recognized antigen. The adaptive immune response requires precise coordination between T and B lymphocytes and is conventionally divided into cell-mediated and humoral immunity.

The humoral response, which leads to antibody production, is initiated either by antigenic or non-antigenic stimulation. Antigenic stimulation is mediated via the B-cell receptor (BCR) and its co-receptors, whereas non-antigenic stimulation occurs through mechanisms such as complement activation, Toll-like receptors (TLRs), and other receptors expressed on B cells (Figure 1).

The process of antibody production by B lymphocytes is regulated by numerous factors. Classical examples include BAFF and APRIL, which are synthesized by myeloid cells such as monocytes, macrophages, and dendritic cells (Mathur et al. 2023; Cheung et al. 2024). BAFF exists in both transmembrane and soluble forms, the latter generated via proteolytic

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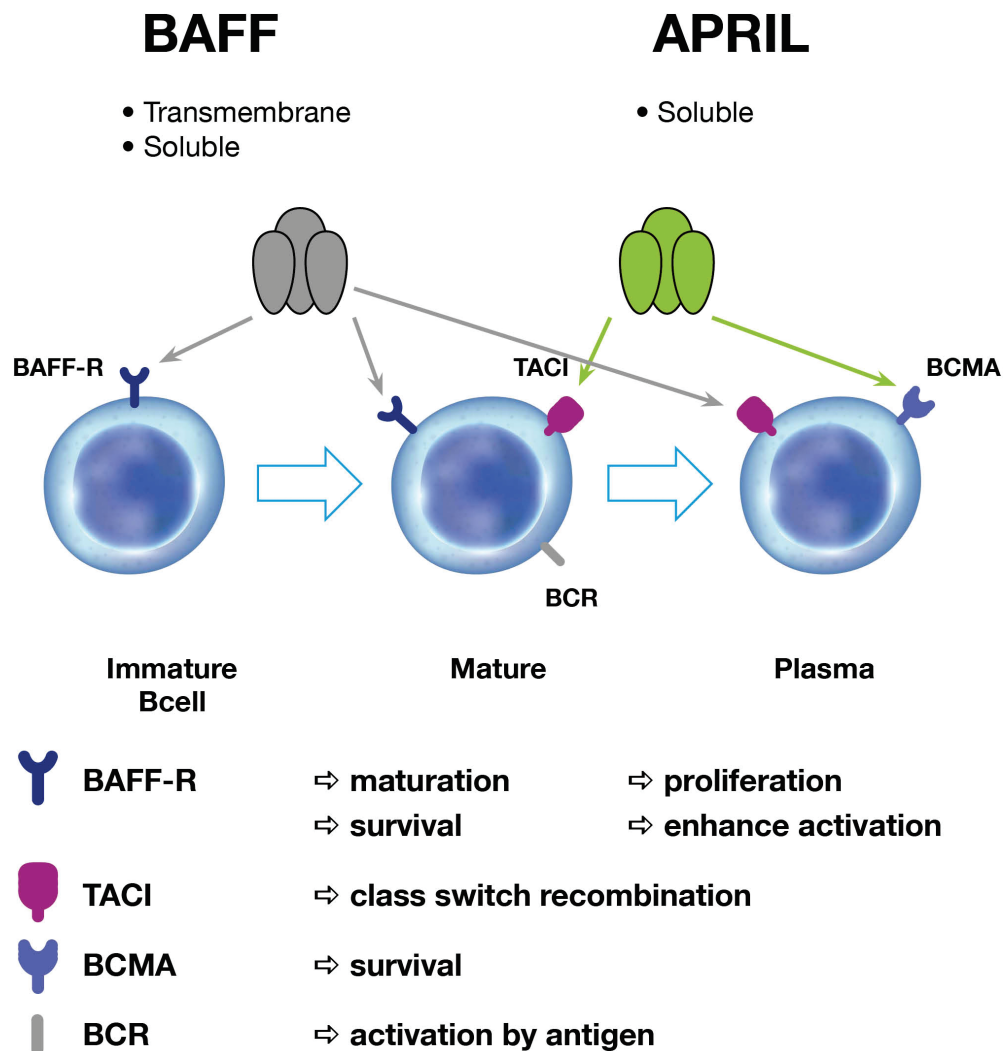


Fig 1. The overall view on the roles of BAFF and APRIL in B lymphocyte life-cycle. APRIL, A Proliferation-Inducing Ligand; BAFF, B-cell-activating factor; BAFF-R, BAFF receptor; BCMA, B-cell maturation antigen; BCR, B-cell receptor; TACI, Transmembrane activator and calcium-modulator and cyclophilin ligand interactor.

cleavage, whereas APRIL is initially membrane-bound and later circulates as a trimeric molecule. These cytokines interact with three receptors belonging to the tumor necrosis factor (TNF) receptor family:

- BAFF receptor (BAFF-R): Expressed on immature (transitional) and mature B cells, it promotes B-cell survival and maturation.
- Transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI): Found on mature B cells and plasma cells, it mediates class-switch recombination and can exert both positive and negative effects on B-cell responses.
- B-cell maturation antigen (BCMA): Expressed primarily on plasma cells, it regulates their survival and supports long-lived antibody production.

Once B lymphocytes are activated by antigens via the BCR, sustained activation is achieved through co-stimulation by T cells (via the CD40 ligand) and BAFF-R, which promotes B-cell maturation, survival, and proliferation. Mature B cells are further stimulated by the TACI receptor, which facilitates antibody class switching and interacts with both BAFF and APRIL. Additionally, plasma cells express BCMA receptors, which enhance their survival.

1.1. The role of BAFF and APRIL in autoimmunity

In the pathogenesis of many autoimmune conditions, either T-cell- or B-cell-driven mechanisms predominate. In psoriasis, ankylosing spondylitis, and Hashimoto's thyroiditis, where antibodies do not play a causative role, targeted treatments should focus on T-cell regulation.

Conversely, in B-cell-mediated disorders such as SLE, SS, RA, myasthenia gravis, and, to some extent, multiple sclerosis, therapeutic strategies aimed at modulating humoral immunity are more appropriate. Interestingly, sera from these patients are characterized by elevated levels of BAFF and APRIL. When specific pathogenic antibodies are present, their levels correlate with disease severity (Samy et al. 2017). Indeed, in BAFF-transgenic (Tg) mice, a lupus-like disease was observed, characterized by splenomegaly, lymphadenopathy, increased production of anti-dsDNA and anti-nuclear antibodies, and enhanced renal immunoglobulin complex deposition (Khare et al. 2000). This effect appears to be independent of T cells and is mediated through TLRs, whose expression is regulated by TACI (Groom et al. 2007). Loss of TACI expression prevents class-switched autoantibody production and protects against BAFF-driven autoimmune tissue damage without significantly reducing B-cell numbers (Figgett et al. 2015). In a subsequent study, the authors proposed the combined targeting of BAFF-R and TACI or BAFF-R and BCMA as a therapeutic approach for SLE (Jacob et al. 2015). An alternative strategy involving selective antibody-mediated APRIL blockade was shown to reduce anti-dsDNA and anti-chromatin autoantibody levels and prevent proteinuria in a mouse model of SLE (Huard et al. 2012).

Other autoimmune disorders are also characterized by increased B-cell activity; however, the upregulation of BAFF and APRIL is not as straightforward as in SLE. In early RA, elevated serum BAFF levels—which are associated with synovitis and diminish with treatment—have been observed (Bosello et al. 2008). However, synovial APRIL concentrations are similar between RA and non-RA patients. The key difference lies in the presence of APRIL-producing cells (e.g., neutrophils) in the inflamed synovium compared to healthy individuals, although this finding is not specific to RA (Gabay et al. 2009). Similarly, SS patients exhibit higher-than-normal serum BAFF titers, but BAFF expression in salivary gland tissue is comparable to that in healthy volunteers. In contrast, expression of APRIL and TACI in SS patients is even decreased (Vosters et al. 2012).

Elevated serum BAFF and APRIL levels have also been reported in patients with immunoglobulin G (IgG)4-related disease. During treatment, BAFF concentrations decrease, while APRIL levels increase, indicating that further studies are needed to understand this interplay (Kiyama et al. 2012).

2. BAFF and APRIL in the Kidneys

BAFF and APRIL are primarily produced by myeloid cells, while their receptors are localized on B lymphocytes.

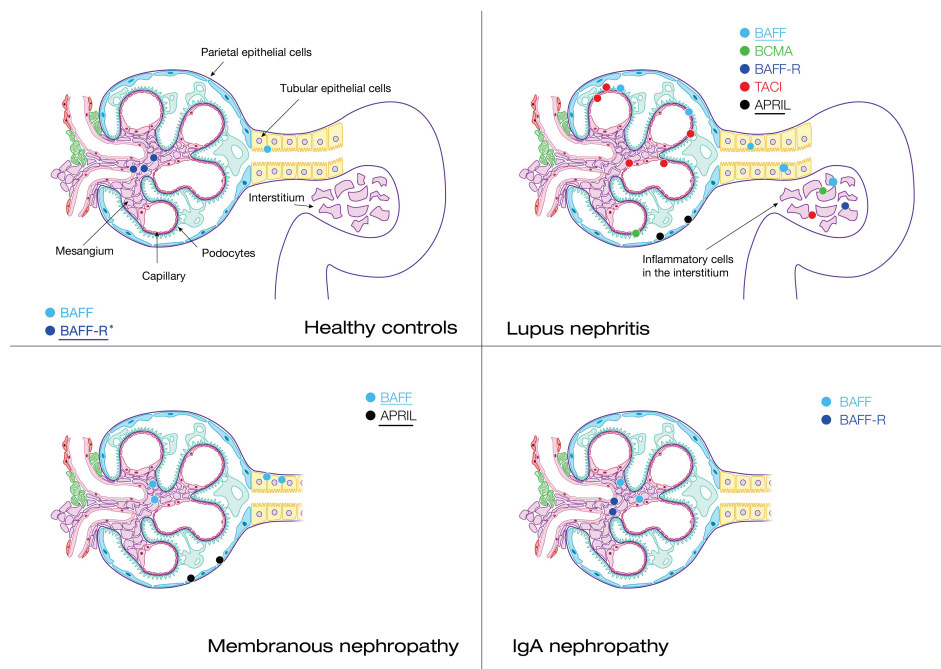


Fig 2. The expression of B-cell activation receptors and molecules reported in various studies. Underlined data come from mRNA analysis. *Identified both by mRNA and immunohistochemistry analysis (Zheng et al. 2015; Han et al. 2018; Cao et al. 2020; Forero-Delgadillo et al. 2022; Marin-Rosales et al. 2022). Both immunohistochemistry staining and mRNA expression were used in independent research, which probably influence incoherent results. APRIL, A Proliferation-Inducing Ligand; BAFF, B-cell-activating factor; BAFF-R, BAFF receptor; BCMA, B-cell maturation antigen; TACI, Transmembrane activator and calcium-modulator and cyclophilin ligand interactor.

Additionally, BAFF-R is expressed on the cell membrane of human mesangial cells. Activation of these receptors leads to mesangial cell proliferation, whereas blocking BAFF/BAFF-R binding inhibits this effect (Zheng et al. 2015). Since mesangial proliferation is an unfavorable prognostic factor in most types of GN, local upregulation of BAFF production may have a detrimental effect on the progression of chronic kidney disease. Evidence also suggests that BAFF levels are elevated either systemically or locally in certain types of GN, such as IgAN and LN (Zheng et al. 2015). In the glomeruli of patients with proliferative LN, APRIL and BAFF mRNA levels were found to be 12-fold and 30-fold higher, respectively, compared to pretransplant biopsies of living donors. Subsequent immunohistochemical staining demonstrated significant APRIL protein expression in 11 of 21 biopsies, localized in the tubulointerstitium, parietal epithelial cells, and at the vascular pole of the glomeruli. In contrast, biopsies from membranous nephritis patients were mostly negative for APRIL. Despite the increased mRNA expression, BAFF protein was detected only in inflammatory infiltrates in the tubulointerstitium, co-expressed with BCMA and TACI (Neusser et al. 2011). Figure 2 illustrates the distribution of B-lymphocyte-activating receptors as reported in various studies. Notably, some discrepancies—such as the presence of BAFF-R receptors in healthy controls and their absence in GN patients—are likely due to methodological differences (e.g., immunohistochemistry vs. mRNA expression analysis) or small patient sample sizes. Immunohistochemical staining is less precise but can be performed on archived biopsy tissues, whereas mRNA expression analysis is more objective but requires specialized tissue preparation and greater financial resources. To our knowledge, no direct comparison of BCR expression in IgAN, LN, and membranous nephropathy (MN) has been published. This underlines the need for further studies, particularly as more advanced tissue examination methods become available. The future of receptor expression research may lie in spatial transcriptomics, a technique capable of identifying active genes in samples as small as three glomeruli. For instance, the molecular profiles of patients with IgAN and mesangial proliferation have been shown to exhibit significantly higher expression of genes involved in adhesion molecules, vascular development, and extracellular matrix formation compared to controls with non-proliferative forms of IgAN.

2.1. IgAN

A key susceptibility locus for IgAN identified by genome-wide association studies (GWAS) is located on chromosome 17p13, where APRIL and other immune regulatory genes are found (Yu et al. 2011; Kiryluk et al. 2014). The genes encoding

APRIL (TNFSF13) and its receptor TACI (TNFRSF13B) likely contribute to IgAN predisposition. TNFSF13 activity is induced by intestinal bacteria, leading to elevated APRIL levels and CD40-independent class switching. Mutations in TNFRSF13B (TACI) can result in IgA deficiency or common variable immunodeficiency, conditions associated with increased susceptibility to mucosal infections (Yu et al. 2011; Kiryluk et al. 2014; Sallustio et al. 2021).

In addition to immune cells, small amounts of BAFF-R are expressed in other tissues, including the cell membranes of human mesangial cells (Zheng et al. 2015). *In vitro*, BAFF-R/BAFF interaction has been shown to promote mesangial cell proliferation by activating the TRAF6/NF- κ B signaling pathway and increasing the expression of fibroblast-associated factors in the kidney (Cao et al. 2020). However, this effect was minor, and it remains unclear whether it contributes to cell damage *in vivo*.

In animal studies, excess BAFF promotes B-cell subset expansion and induces autoimmune disease features resembling SLE and SS (McCarthy et al. 2011). In BAFF-overexpressing Tg mice, lifespan was shortened and severe or fatal nephritis developed by 17 months of age. A sex-specific effect was observed, with males exhibiting both higher BAFF levels and faster disease onset. With age, they developed albuminuria exceeding 300 mg/dL and IgA mesangial deposition in the glomeruli. Unlike traditional SLE mouse models (NZB \times NZW F1), these mice exhibited minimal IgG and C4 glomerular deposits, suggesting a distinct pathophysiology. Mesangial proliferation was only occasionally observed, pointing toward a B-cell-mediated injury mechanism.

Interestingly, commensal gut flora plays a crucial role in elevated serum IgA levels. Antibodies reactive against commensal bacteria have been detected in the blood of BAFF-Tg mice, suggesting that microbial signals drive serum hyper-IgA and renal IgA deposition in this model (McCarthy et al. 2011). Additionally, when BAFF-Tg mice were nasally infected with *Neisseria meningitidis*, they developed anti-*Neisseria*-specific IgA-secreting cells within their kidneys (Currie et al. 2022).

In humans, serum BAFF and APRIL levels have been confirmed to be elevated in IgAN patients compared to healthy controls. Moreover, BAFF levels correlate with increased proteinuria, while APRIL levels are inversely correlated with estimated glomerular filtration rate (eGFR) (Xin et al. 2013; Sallustio et al. 2021). Elevated serum BAFF in IgAN is associated with specific histopathological findings, including mesangial hypercellularity and segmental glomerulosclerosis, as well as the severity of tubular atrophy and interstitial fibrosis (Xin et al. 2013). Furthermore, IgAN patients tend to have elevated APRIL levels, which correlate with disease severity, including proteinuria and eGFR decline. Increased APRIL expression is also associated with higher levels of galactose-deficient IgA1 (Gd-IgA1)—a prognostic marker

linked to long-term renal function decline in IgAN (Zhai et al. 2016).

The 4-Hit hypothesis of IgAN pathogenesis proposes that initially some individuals have elevated levels of Gd-IgA1 (Hit 1), which may be partially attributed to gut dysbiosis. This condition increases intestinal wall permeability and activates gut-associated lymphoid tissue. An unknown trigger leads to the production of auto-antibodies against Gd-IgA1 (Hit 2). This, in turn, results in the formation of circulating immune complexes (Hit 3) that precipitate in the glomerular mesangium, inducing further inflammatory reactions (Hit 4), ultimately damaging the kidney [Suzuki et al. 2011; summarized by Mucha et al. (2023)]. Since APRIL is responsible for IgA class switching and the survival of IgA-plasma-secreting cells, targeting APRIL is a logical therapeutic strategy. Some drugs currently being tested for IgAN have been adapted from SLE studies:

- Atacicept, a recombinant fusion protein that blocks TACI, inhibiting both BAFF and APRIL signaling (Lafayette et al. 2024).
- Telitacicept, which similarly acts on the TACI receptor (Cai et al. 2023).
- Povetacicept, an antagonist of both APRIL and BAFF (Evans et al. 2023).

Other biologics specifically developed for IgAN include sibeprenlimab (Mathur et al. 2024) and zigakibart (Trimarchi et al. 2024), both of which are humanized antibodies that block APRIL. All these drugs have shown significant reduction in proteinuria; for example, sibeprenlimab produced a dose-dependent reduction in proteinuria of 47.2%–62% after 12 months of use (detailed description by Selvaskandan et al. (2023)). These treatments may also be applicable for other types of GN.

Promising Phase II results will require further evaluation in Phase III studies. Ongoing trials for sibeprenlimab (VISIONARY; NCT05248646), zigakibart (BEYOND; NCT05852938), telitacicept (NCT05799287), atacicept (ORIGIN 3; NCT04716231), and povetacicept (RUBY 3; NCT05732402) are currently in Phase III, with expected completion by the end of 2026.

2.2. MN

MN is closely associated with B lymphocytes, and reducing their number has become a first-line treatment option (e.g., rituximab [RTX]). However, several areas of uncertainty remain regarding the B-cell response at the molecular level. First, no polymorphisms conferring genetic susceptibility in BAFF, TACI (TNFRSF13B), or APRIL (TNFSF13) have been described to date. Second, the diversity of MN subtypes complicates research on this rare condition. The terms “primary” and “idiopathic MN” are no longer considered precise enough and have been replaced by PLA2R-positive

and PLA2R-negative MN. The PLA2R-negative type may depend on other antigens such as thrombospondin type-1 domain-containing 7A (THSD7A), exostatin1/exostatin2 (EXT1/EXT2), neuronal epidermal growth factor-like 1 protein (NELL-1), semaphorin-3B (Sema-3B), neural cell adhesion molecule 1 (NCAM-1), high-temperature recombinant protein A1 (HTRA1), and protocadherin 7 (PCDH7) (Caza et al. 2023). Not all of these antigens have corresponding antibodies detectable in blood or tissue. It remains unclear whether PLA2R-mediated MN shares a similar pathogenetic background with other types of MN.

In the study by Han et al. (2018), MN patients had higher plasma BAFF levels than healthy subjects. Interestingly, BAFF levels were more elevated in secondary MN compared to primary MN; however, this study did not include a PLA2R-based classification. APRIL levels were similar between MN patients and healthy controls. On the other hand, in a study by Han et al. (2018), glomerular BAFF mRNA expression was similar to that of the healthy control group, while glomerular APRIL mRNA expression was comparable to that observed in LN and higher than in healthy controls. Tubular expression of both BAFF and APRIL was increased in the LN group and low in MN and healthy controls (Han et al. 2018).

BAFF and APRIL seem to correlate with disease activity. In a retrospective study by Netti et al. (2019), serum BAFF levels were significantly higher in PLA2R-positive MN and in LN grade III and IV patients compared to those without anti-PLA2R antibodies. Furthermore, BAFF and APRIL levels tend to decrease in individuals who achieve remission after immunosuppressive therapy and persist in patients with sustained disease activity (Netti et al. 2019). BAFF and APRIL levels are also correlated with PLA2R levels and, similarly to PLA2R, predict remission (Li et al. 2024). Ongoing trials are evaluating belimumab, a BAFF inhibitor approved for LN, in PLA2R-positive MN. Thus far, other agents targeting BAFF and APRIL blockade have not been widely used in MN. However, this may soon change as the first case reports of successful treatment with APRIL inhibitors, such as telitacicept, have already been published (Zhang et al. 2023).

3. Treatments Targeting B Cells in Glomerulopathies

In B-cell-related diseases, several strategies have been explored. One key approach involves targeting B lymphocytes by eliminating cells expressing the CD20 marker. RTX, a chimeric monoclonal antibody, has been widely used in various antibody-mediated conditions. In the European Union, RTX is registered for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia (CLL), RA, granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris (Union Register of Medicinal Products – Public Health – European Commission 2024). It is also the first-line

treatment in high-risk PLA2R-positive MN. Despite its ability to lower dsDNA antibody levels, RTX failed to meet primary endpoints in two major trials: EXPLORER, which focused on non-renal SLE and LUNAR, which evaluated its effectiveness in LN. This failure may be attributed to inadequate depletion of CD19⁺ B cells or the high variability of pathogenic mechanisms involved in SLE, such as autoreactive B cells, alterations in TLR receptor function, differences in the interferon (IFN)- α pathway, or T-cell dysfunction (Mo et al. 2024). Tailoring treatment to the dominant mechanism in a specific patient (for example, by measuring BAFF levels) could, in theory, bring better results. So far, RTX is recommended by the European Alliance of Associations for Rheumatology and the American College of Rheumatology for refractory lupus, based mostly on observational data (Piantoni and Korsten 2022). Unfortunately, RTX has not proven efficacious in IgAN. It failed to reduce proteinuria, serum levels of Gd-IgA1, or antibodies against Gd-IgA1. Moreover, no significant difference in eGFR was observed. Whether these outcomes are due to the activity of plasma cells escaping RTX-induced cytotoxicity or the involvement of the mucosal immune system remains unknown (Lafayette et al. 2017).

The second- and third-generation anti-CD20 antibodies, including humanized (ocrelizumab, obinutuzumab) and fully human (ofatumumab) antibodies, may prove more effective than RTX, a first-generation anti-CD20 antibody (Roos et al. 2023). These newer generations are glycoengineered to enhance binding to immune effector cells (e.g., natural killer cells), as well as improve direct or Ab-dependent cellular cytotoxicity and complement-dependent toxicity. RTX is a chimeric murine-human antibody, which can trigger anti-drug antibodies (ADA), reducing its efficacy over time. Humanized or fully human antibodies decrease the likelihood of ADA development, potentially leading to less resistance and sustained efficacy. Newer agents may allow dose adjustments or subcutaneous administration (e.g., ofatumumab), which can help in achieving more consistent drug levels.

For example, in a head-to-head comparison with RTX in multiple sclerosis, patients treated with ocrelizumab had a lower rate of relapses than those treated with RTX. In a newly published study, obinutuzumab demonstrated higher complete renal response (CRR) rates (defined as urine protein-creatinine ratio [UPCR] <0.5 , no worsening of baseline serum creatinine by $>15\%$, and inactive urinary sediment) than standard therapy alone in class III and IV LN. CRR at week 76 was achieved by 42.7% vs. 30.9% in the placebo + standard therapy group, and a UPCR <0.8 was seen in 55.5% vs. 41.9% (Furie et al. 2025). In a previous trial, the results were similar, with 35% vs. 23% of patients achieving CRR (Furie et al. 2022a). In the 2025 study, serious adverse events occurred in 32.4% of patients in the obinutuzumab group and in 18.2% in the placebo group. The most frequent serious adverse events were infections, including Covid-19,

urinary tract infection, pneumonia, and gastroenteritis. The authors concluded that obinutuzumab presented a good safety profile, but the decision to double the risk of serious adverse events in order to increase the chance of CRR by approximately 10% remains a difficult one. Alternative strategies for targeting B cells beyond anti-CD20 therapies may be necessary.

Belimumab, a monoclonal antibody targeting the soluble form of BAFF, is the first biological drug approved for SLE. A comprehensive review of published clinical trials (real-world effectiveness) reported a reduction in disease activity, measured by the SELENA-SLEDAI score, 10.1–4.4 points (Huang et al. 2022). Belimumab is also the only biological agent registered for the treatment of LN; however, the results are not groundbreaking. A CRR and an eGFR no more than 10% below the open-label baseline value or ≥ 90 mL/min per 1.73 m^2 was achieved in only 30% of patients compared to 20% in the placebo group after 104 weeks of treatment (Furie et al. 2020). In a two-year extension of this trial, the proportion of patients with CRR increased from 36% to 48% in the placebo-to-belimumab group and from 48% to 62% in the belimumab-to-belimumab group (Furie et al. 2022b). Even though belimumab did not prove to be a groundbreaking medication in LN and is recommended by EULAR in induction or maintenance therapy of LN only in combination with other agents (mycophenolate, low-dose cyclophosphamide, or azathioprine), its strength may lie in its steroid-sparing effect (Worley et al. 2023). No other biological agent has been registered for the treatment of LN so far.

As B-cell activation is dependent on BAFF, TACI, and the BCR receptor, dual inhibition should, in theory, offer improved efficacy. Atacicept is a recombinant human TACI-immunoglobulin fusion protein that binds to both BAFF and APRIL. In a study evaluating atacicept in SLE, atacicept reduced the incidence of severe flares, disease activity as measured by various indices, and anti-dsDNA antibody levels. However, it did not significantly increase the proportion of patients achieving a corticosteroid dosage reduction to ≤ 7.5 mg/day. No information regarding proteinuria and eGFR was available (Wallace et al. 2021). Unfortunately, a new study on atacicept in patients with active LN (COMPASS, NCT05609812), has been suspended due to business reasons.

Both belimumab and atacicept have relatively good safety profiles. 74.5% of belimumab-treated patients experienced an infection during 76 weeks of study, compared to 69% on placebo, with a similar rate of serious infections (7% vs. 5.8%, respectively). Hypogammaglobulinemia occurred in only 1 of 544 patients (Furie et al. 2011). Infections with atacicept were reported in 46.4% of patients compared to 43.6% in the placebo group, while hypogammaglobulinemia occurred in only 6 of 1085 patients (Gordon et al. 2019). This is significantly lower than the rate reported with RTX, which could be explained by the fact that BAFF and APRIL inhibitors reduce

Table 1. Biological agents targeting BAFF and APRIL

Name	Target	Mode of action	Potential application	Research phase	References
Belimumab	Soluble BAFF	Monoclonal antibody	Approved in SLE, trials in PLA2R + MN	Phase 2 NCT03949855	Huang et al. (2022)
Blisibimod	Soluble BAFF	Peptibody	SLE	No ongoing trials	Chan et al. (2023)
Tabalumab	Soluble and membrane-bound BAFF	Human monoclonal antibody	SLE	No ongoing trials	Chan et al. (2023)
Ianalumab	BAFF-R on B cells	Monoclonal antibody	SS, SLE	Phase 3 in SLE: NCT06711887 NCT06133972 Phase 3 in SS: NCT05985915	Bowman et al. (2022)
Atacicept	BAFF and APRIL	Fusion protein (TACI receptor + Ig fragment)	SLE, IgAN	Phase 3 in IgA: NCT04716231 Phase 2 in IgA: NCT06674577	Lafayette et al. (2024)
Telitacicept	BAFF and APRIL	Fusion protein TACI-Fc	IgAN, MN SLE	Phase 2 in MN: NCT06614985 Phase 3 in SLE: NCT06456567	Cai et al. (2023) and Zhang et al. (2023)
Sibeprenlimab	APRIL	Humanized IgG2 monoclonal antibody	IgAN	Phase 2 in IgA: NCT06740526	Mathur et al. (2024)
BION-1301 (Zigakibart)	APRIL	Monoclonal antibody	IgAN	Phase 3 in IgA: NCT06858319 NCT05852938	Barratt et al. (2023)

APRIL, A Proliferation-Inducing Ligand; BAFF, B-cell-activating factor; BAFF-R, BAFF receptor; IgAN, IgA nephropathy; IgG, immunoglobulin G; MN, membranous nephropathy; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; TACI, Transmembrane activator and calcium-modulator and cyclophilin ligand interactor.

B-cell function and antibody production more selectively, without directly depleting B cells through complement activation or antibody-dependent cellular cytotoxicity (Benson et al. 2008). The authors' selection of biological agents targeting BAFF and APRIL, along with their potential applications, is presented in Table 1.

Except for rapidly progressive cases with a high percentage of proliferating parietal epithelial cells on kidney biopsy (crescents), the depletion of CD20 cells has not found widespread application in the treatment of IgAN (Zhuang et al. 2023). As GWAS research in IgAN has identified a gene pair encoding APRIL and its receptor as susceptibility loci, most efforts have been focused on targeting this pathway. Sibeprenlimab, a humanized monoclonal antibody that binds to and neutralizes APRIL, demonstrated up to $62.0 \pm 5.7\%$ reduction in the 24-h UPCR at 12 months (Mathur et al. 2024). Zigakibart, another humanized monoclonal antibody that blocks APRIL, produced clinically meaningful reductions in proteinuria, with 7 out of 8 patients achieving a $>50\%$ decrease in UPCR from baseline at week 52 (Barratt et al. 2023). Dual blockade by telitacicept, a fusion protein combining the TACI with the fragment crystallizable portion of IgG, which neutralizes both BAFF and APRIL, also shows promise. In higher doses (240 mg), telitacicept reduced mean proteinuria in IgAN by 49% from baseline compared to placebo, with the effect being dose-dependent. In smaller doses (160 mg), proteinuria reduction reached only 25%. Importantly, eGFR remained stable, and adverse events were similar in both

groups (Lv et al. 2023). Likewise, atacicept resulted in a 25% reduction of UPCR vs. placebo at 24 weeks, with stabilization of eGFR at week 36. This was associated with a mean geometric difference of 11% between groups, corresponding to approximately 5.7 mL/min/1.73 m² (Lafayette et al. 2024). Interestingly, no studies have reported on the effectiveness of sole BAFF blockade by belimumab in IgAN. Results from the BRIGHT-SC study (estimated primary completion in October 2016), investigating the impact of blisibimod, a BAFF inhibitor, on proteinuria in IgAN, were never published.

4. Chimeric Antigen Receptor T (CAR-T) Cells and BAFF-R Blockade

CAR-T cells are a cell-based therapy initially developed for cancer and recently showing preliminary efficacy in autoimmune diseases. In this approach, a patient's T cells are collected from the blood through leukapheresis and genetically modified to express a specialized receptor known as CAR. This receptor is designed to recognize a specific antigen, subsequently activating the T cells to destroy the target cells. While originally used in cancer treatment, CAR-T cells can be engineered to target various antigens, including BAFF-R. However, the application of CAR-T therapy is currently restricted to the most severe conditions, such as hematological malignancies and refractory, life-threatening autoimmune diseases, due to potentially life-threatening side effects associated with this treatment. One major

complication of CAR-T cell therapy is cytokine release syndrome (CRS), a condition characterized by a cytokine surge that can occur shortly after the infusion of CAR-T cells. CRS can manifest as fever, hypoxia, hypotension, and life-threatening multi-organ failure. The incidence of CRS can vary, occurring in 40%–100% of patients, depending on the type of CAR-T cells used (Xiao et al. 2021). Additionally, CAR-T cell therapy may be complicated by the development of T-cell lymphoma. Retroviral or lentiviral vectors, which are used to insert genetic material into T cells, may, in rare cases, disrupt tumor suppressor genes or activate oncogenes, leading to the development of T-cell malignancies. Lastly, CAR-T therapy requires conditioning with fludarabine and cyclophosphamide, which are associated with hematological toxicity, increased susceptibility to infections, and an elevated risk of malignancies. With these precautions in mind, CAR-T cells might find use in certain autoimmune conditions.

The first trials targeting B lymphocytes in autoimmune diseases have already been published, and the results, especially in SLE, are promising. In one case, a 20-year-old woman with severe and refractory SLE, who was unresponsive to both RTX and belimumab, achieved clinical remission after receiving an infusion of autologous CD19 CAR T cells. Her SLEDAI score decreased from 16 to 0 (Mougiakakos et al. 2021). In a case series involving five SLE patients with active, refractory disease, anti-CD19 CAR-T cell therapy resulted in a significant improvement in clinical symptoms and normalization of laboratory parameters, including the seroconversion of anti-dsDNA antibodies (Mackensen et al. 2022). A Phase 1 clinical trial treated 12 patients with refractory SLE using CD19/BCMA CAR-T cells with a median follow-up of 118.5 days (range: 45–524 days). Despite all patients developing CRS and one-third experiencing infections, all patients recovered after treatment. The SLEDAI-2K score decreased from a mean of 18.3 to 1.5 (Feng et al. 2023). In a study by Wang et al. (2024) 13 LN patients were treated with BCMA and CD19-directed CAR-T cells, resulting in a reduction of the mean SLEDAI score from 10.6 to 2.7 after 3 months, with a significant improvement in renal function in 10 out of 13 patients. The therapy was well tolerated, with only mild CRS observed (Wang et al. 2024).

As stated previously, BAFF binds the three receptors: BAFF-R, BCMA, and TACI. In case of a disease relapse

due to the loss of the CD19 antigen, as sometimes occurs in leukemia, BAFF-CAR-T cells could offer additional therapeutic benefits, as almost all B-cell cancers are reported to express at least one of these receptors (Wong et al. 2022). BAFF CAR-T cells can successfully bind to each of the three BAFF-Rs and effectively destroy B-cell cancers, including mantle cell lymphoma, multiple myeloma, and acute lymphoblastic leukemia (ALL) *in vitro* and *in vivo* in xenograft models (Wong et al. 2022). Additionally, a BAFF-R CAR against CLL cells (MC10029) was tested in mice, resulting in 100% survival after 84 days (Luo et al. 2023). In another study, a dual CAR construct targeting both CD19 and BAFF-R achieved complete eradication of ALL cells in a mouse model, showing an advantage over monospecific CD19 or BAFF CAR-T therapies, where relapse occurred (Wang et al. 2022). Table 2 presents ongoing trials of CAR-T cells targeting the BAFF molecule. However, to date, no APRIL-targeting CAR-T lymphocytes have been developed.

CAR-T cells primarily affect circulating cells, such as B lymphocytes, and are capable of active penetration into tissues to some extent, an advantage over monoclonal antibodies, which do that solely by diffusion. CAR-T cells are able to penetrate lymph nodes and induce deep-tissue depletion of B cells. Whether this is sufficient to affect the mesangial cells is yet unknown. The majority of kidney injury after CAR-T cell therapy stems from CRS, and cases of glomerular injury are extremely rare. The expression of BAFF, along with IFN- α and IL-12, on renal immune cells is significantly higher in patients with proliferative LN compared to those with IgAN, LN class II, or healthy controls. Notably, the local increase in IFN- α and IL-12 correlates with the presence of active lesions, a poorer prognosis (for IFN- α), and a higher tubular atrophy score (for IL-12). In contrast, BAFF predominance is associated with a lower modified National Institute of Health total index and activity index, fewer cases of class IV LN, and a better overall prognosis. However, this could reflect the fact that BAFF expression tends to occur in the earlier stages of the disease (Nawata et al. 2023).

Currently, no trials involving CAR-T cells have been carried out or are in planning for IgAN and MN. The high risks associated with CAR-T therapy, combined with the relatively low risk of end-stage kidney failure and low mortality rates in these conditions, make CAR-T a less attractive option for these diseases.

Table 2. Recruiting trials involving BAFF-CAR-T cells in autoimmune conditions

Trial and CAR-T type	Condition	Location	Trial number
Phase I/II open-label, interventional single-arm trial of MB-CART19.1	Refractory SLE	Germany	NCT06189157
Phase I/II, interventional, 4SCAR-T	Autoimmune diseases	China	NCT05459870
Early Phase I, interventional, CD19-BAFF CAR-T	SLE, systemic sclerosis, dermatomyositis, immune nephritis, neuromyelitis optica	China	NCT06279923

BAFF, B-cell-activating factor; CAR-T, chimeric antigen receptor T; SLE, systemic lupus erythematosus.

However, the further development of CAR-T cells targeting specific populations of B cells in tissues could provide a highly desirable treatment approach. If such therapies become feasible, and based on the efficacy of current biological treatments, anti-BAFF therapies may offer better outcomes for MN, while anti-APRIL therapies could be more suitable for IgAN.

5. Conclusions

There is still much to discover about the activation of B lymphocytes and the survival of plasma cells in kidney diseases. Further studies are needed to understand the role of plasma-blasts in various GN types, the involvement of BAFF-Rs in kidney tissue, and the differences between MN with and without PLA2R antibodies. Gaining deeper insights into these processes will enhance our understanding of incomplete remission or persistent disease activity despite aggressive treatment. In the future, a combination of agents targeting plasma and B cells—including CAR-T cells—along with complement system inhibitors might be indicated for patients with particularly resilient types of GN. Agents that inhibit both BAFF and APRIL, such as atacicept or telitacept, should theoretically be more effective than belimumab by preventing B-cell activation via alternative receptors. No evidence currently exists supporting the efficacy of belimumab in IgAN, whereas both telitacept and atacicept have been reported to reduce proteinuria in IgAN. However, these results require validation through head-to-head trials, as not all reports are entirely optimistic. For instance, an observational study comparing LN patients treated with belimumab

or telitacept found no significant difference in kidney parameters after 52 weeks of follow-up (Jin et al. 2025). This suggests that sole B-cell targeting may not be effective in LN. Measuring B-cell activity, such as BAFF levels, could help identify patients who would most benefit from B-cell depletion. While CAR-T cells offer a powerful option for refractory or life-threatening diseases, their use remains limited due to safety concerns. Biological drugs, on the other hand, present a safer option for autoimmune conditions with a moderate risk of end-organ damage, such as IgAN or MN.

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Author Contributions

B.M. wrote the paper. R.Z. and K.M. provided substantive support, the idea for the topic, verified and accepted the paper. R.K. corrected the paper and provided valuable comments.

Conflicts of Interest

The authors declare no conflicts of interest.

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