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CKJ Review



CKJ REVIEW

# The contribution of a proliferation-inducing ligand (APRIL) and other TNF superfamily members in pathogenesis and progression of IgA nephropathy

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## ABSTRACT

Advances in our understanding of the pathogenesis of immunoglobulin A nephropathy (IgAN) have led to the identification of novel therapeutic targets and potential disease-specific treatments. Specifically, a proliferation-inducing ligand (APRIL) has been implicated in the pathogenesis of IgAN, mediating B-cell dysregulation and overproduction of pathogenic galactose-deficient IgA1 (Gd-IgA1). Animal and clinical studies support the involvement of APRIL in the pathogenesis and progression of IgAN. An elevated level of APRIL is found in IgAN when compared with controls, which correlates with the level of Gd-IgA1 and associates with more severe disease presentation and worse outcomes. Conversely, anti-APRIL therapy reduces pathogenic Gd-IgA1 and IgA immune complex formation and ameliorates the severity of kidney inflammation and injury. Genome-wide association studies in IgAN have identified *TNFSF13* and *TNFRSF13B*, a cytokine ligand-receptor gene pair encoding APRIL and its receptor, respectively, as risk susceptibility loci in IgAN, further supporting the causal role of the APRIL signalling pathway in IgAN. Several novel experimental agents targeting APRIL, including atacicept, telitacicept, zigakibart and sibeprenlimab, are currently under investigation as potential therapies in IgAN. Preliminary results suggest that these agents are well-tolerated, and reduce levels of Gd-IgA1, with corresponding improvement in proteinuria. Further studies are ongoing to confirm the safety and efficacy of anti-APRIL approaches as an effective therapeutic strategy in IgAN.

**Keywords:** APRIL, B cells, galactose-deficient IgA1, IgA nephropathy, pathogenesis

## INTRODUCTION

Immunoglobulin A nephropathy (IgAN) is the most common pattern of primary glomerulonephritis worldwide, with an estimated incidence of at least 2.5 cases in every 100 000 adults and a high prevalence in Asia, Europe and North America [1]. In most affected individuals, it takes a slow but progressive clinical course, resulting in eventual kidney failure in 30%–40% of patients within 20–30 years [2–5]. Recently published data suggest, however, that almost all patients are at risk of progression to kidney failure within their expected lifetime [6]. Current treatment guidelines recommend optimizing supportive therapy, including blood pressure control, a low-sodium diet, smoking cessation and maximum-tolerated blockade of the renin–angiotensin–aldosterone system [7], but significant residual risk of progression remains despite these interventions. The safety and efficacy of systemic corticosteroids in IgAN have

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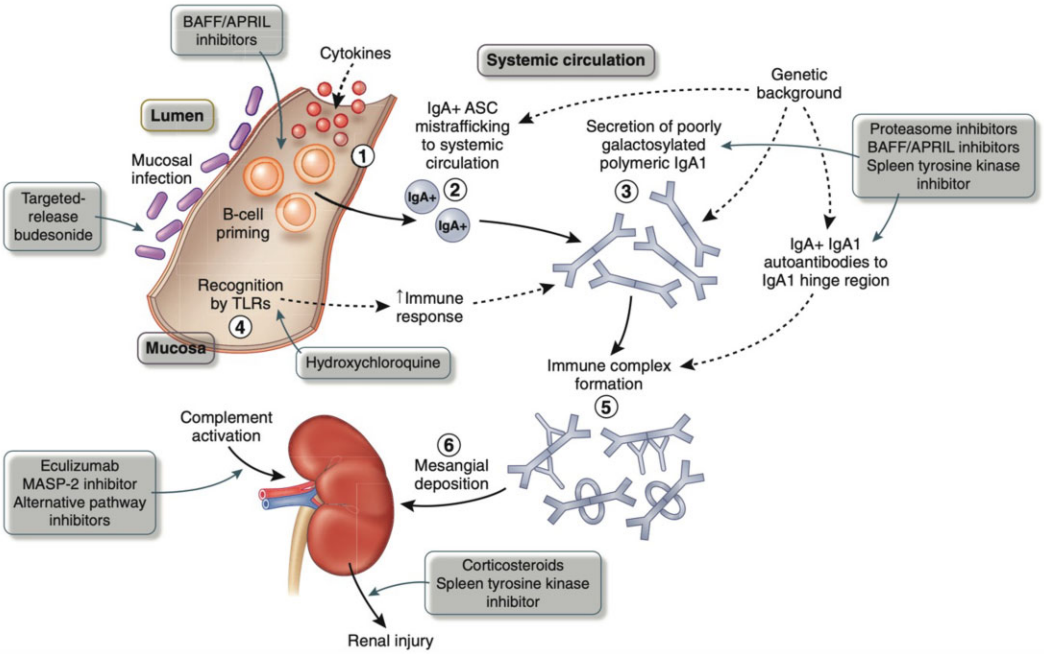


**Figure 1:** Proposed pathogenesis of IgA nephropathy, potential specific therapeutic targets and novel treatment strategies. (1) Mucosal infection primes naïve B cells to class switch to become IgA + antibody secreting cells (ASCs) through T-cell-dependent (cytokine mediated) and T-cell-independent [Toll-like receptor (TLR) ligation] pathways. (2) Some IgA + ASC mis-home to the systemic compartment during lymphocyte trafficking. (3) Displaced IgA + ASCs take up residence in systemic sites and secrete normal 'mucosal-type' poorly galactosylated polymeric (galactose deficient) IgA1 into the systemic circulation. (4) IgA1 secretion by displaced mucosal ASC is augmented by TLR ligation from mucosal-derived pathogen-associated molecular patterns, which have entered the systemic compartment. (5) IgA1 immune complexes form in the systemic circulation. Poorly galactosylated polymeric IgA1 molecules are the substrate for immune complex formation and combine with IgG and IgA autoantibodies reactive to exposed neoepitopes in the poorly galactosylated IgA1 hinge region. (6) IgA1 immune complexes deposit in the mesangium through a combination of mesangial trapping and increased affinity of poorly galactosylated IgA1 for extracellular matrix components. Immune complex deposition triggers a series of downstream pathways leading to glomerular injury and tubulointerstitial scarring. MASP-2, mannan-binding lectin-associated serine protease-2. Reprinted with permission from reference Floege *et al.* [15].

been challenged repeatedly [8–10] and there is currently no evidence to support the broad recommendation of traditional non-specific immunosuppressive agents, such as cyclophosphamide, azathioprine, mycophenolate mofetil and rituximab [11]. A number of novel therapeutic agents are currently being evaluated in IgAN, with some showing promising preliminary results [12, 13]. Given the significant health [6] and economic burden [14], new disease-specific treatments are urgently needed to improve outcomes in IgAN.

While the precise aetiology remains unknown, there have been significant advances in our understanding of the pathogenesis of IgAN, which in turn has led to identification of novel therapeutic targets (Fig. 1) [15]. Broadly, increased levels of circulating poorly *O*-galactosylated polymeric IgA1 [commonly termed galactose-deficient IgA1 (Gd-IgA1)] and the production of *O*-glycan-specific autoantibodies leads to the formation of IgA1-containing immune complexes. Deposition of these complexes in the mesangium results in cellular proliferation, infiltration of inflammatory cells and complement activation, with consequent inflammation and glomerular injury [16]. Given their central roles in the pathogenesis of IgAN, reducing the level of circulating Gd-IgA1 and deposition of IgA1-containing immune complex in the kidney, by targeting B-cell dysregulation, could attenuate disease activity and beneficially alter the course and outcome of the disease [17]. Hence, attention has been directed towards the underlying mechanisms implicated in the production of Gd-IgA1 and its glycan-specific autoantibody. Quantitative trait genome-wide association studies (GWAS) have identified allelic variations in the noncoding region of *C1GALT1* that determine the serum levels of Gd-IgA1 and suggest factors in the local microenvironment may directly control regulation of Gd-IgA1 synthesis [18, 19]. Specifically, the role of a proliferation-inducing ligand (APRIL), a tumour necrosis factor (TNF) superfamily cytokine involved in B-cell signalling [20, 21], and its function in driving IgA class switch recombination and production [22] and survival of IgA-secreting plasma cells [23] has become increasingly acknowledged as likely to play a key role in IgAN.

Here, we will review the APRIL system, its role in the pathogenesis and progression of IgAN, and evidence supporting how the APRIL system has become a therapeutic target in IgAN.

## THE APRIL SYSTEM IN HEALTH AND DISEASE

The APRIL system consists of the ligand APRIL, also known as TNF ligand superfamily member 13, and its two receptors, (i) B-cell maturation antigen (BCMA), also known as TNF receptor superfamily member 17, and (ii) transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), also known as TNF receptor superfamily member 13B (Table 1).

As the name TNF ligand superfamily member 13 suggests, APRIL belongs to the TNF family of cytokines and is involved in various processes of B-cell signalling in the immune system, including the maturation and differentiation of naïve B cells, which are subsequently responsible for producing immunoglobulins [24]. It also acts as a co-stimulatory signal for B cells, promoting their survival and proliferation. Additionally, APRIL

**Table 1: Nomenclature and function of APRIL, BAFF and associated receptors; the nomenclature, alternative names, key functions in general and sub-functions [58] of ligands APRIL, BAFF and its associated receptors, TACI, BCMA and BAFF-R are detailed.**

| | Ligands | | Receptors | | |
|---|---|---|---|---|---|
| Nomenclature | APRIL (a proliferation-inducing ligand) | BAFF (B-cell activating factor of the TNF family) | TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) | BCMA (B-cell maturation antigen) | BAFF-R (BAFF-receptor) |
| Alternative name(s) | TNFSF13<br>TALL-2 (TNF- and ApoL-related leukocyte- expressed ligand-2)<br>TRDL-1 (TNF-related death ligand-1) | TNFSF13B<br>BLyS (B lymphocyte stimulator)<br>TALL-1 (TNF- and ApoL-related leukocyte-expressed ligand-1)<br>THANK (TNF homologue activates apoptosis, NF-$\kappa$B and JNK)<br>zTNF4 (z-tumour-necrosis factor-4) | TNFRSF13B | TNFRSF17 | TNFRSF13C<br>BLyS receptor-3 |
| Key functions<br>(i) Immature B-cell survival and maturation<br>(ii) B-cell regulation<br>(iii) T-cell-independent antibody responses<br>(iv) Class-switch recombination<br>(v) Plasma cell survival | | | | | |
| **Specific sub-function** | | | | | |
| B-cell co-stimulation | Y | Y | ? | ? | Y |
| Plasmablast and plasma cell survival | Y | Y | | Y | |
| Ig class switch | Y | Y | Y | | Y |
| Enhanced B-cell APC function | Y | Y | | Y | |
| T-cell-independent type II responses | Y | Y | Y | | |
| Modulation of T-cell-dependent responses | ? | Y | Y | Y | Y |
| T-cell co-stimulation | ? | Y | ? | | ? |
| B-1 cell function | ? | ? | ? | | ? |
| B-cell development (beyond T-1) | | Y | | | Y |
| Complete germinal centre formation | | Y | Y | Y | Y |

Legend: Y, yes; ?, possible.
APC, antigen presenting cell; TNFSF, tumour necrosis factor super family; TNFRSF, tumour necrosis factor receptor super family.

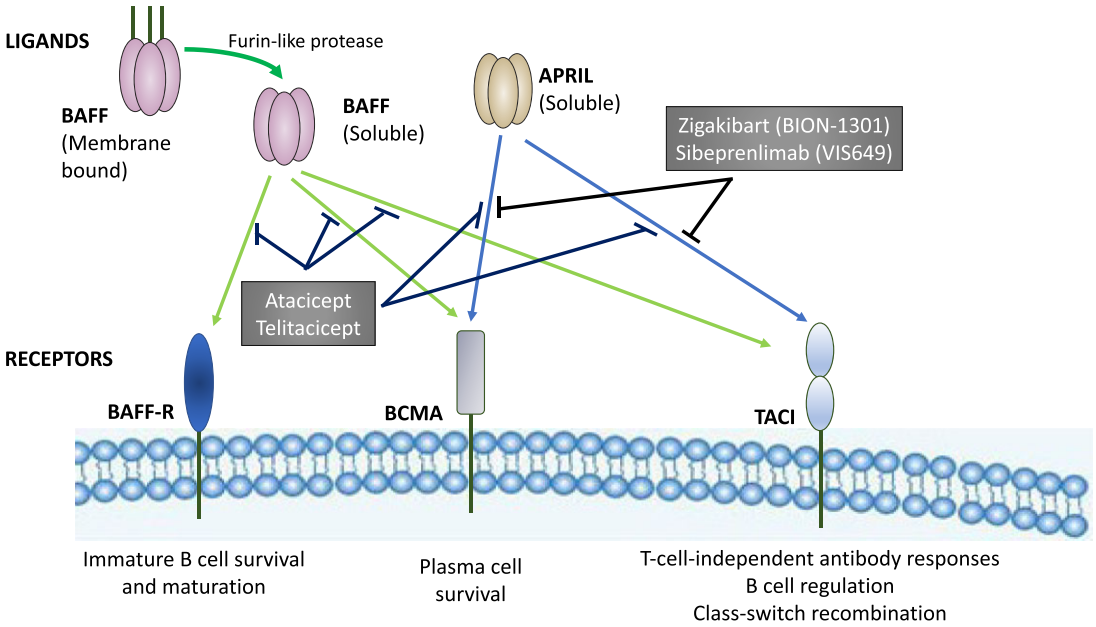


**Figure 2:** APRIL and BAFF with their receptors, BCMA, TACI and BAFF-R, and potential therapeutic targets. The interactions between the soluble ligands APRIL and BAFF (also exists as a membrane bound protein that is cleaved by a furin-like protease to release the soluble form) and their receptors BCMA, TACI and BAFF-R expressed on B cells are shown, along with some of the key functions mediated by these associations. Atacicept and telitacicept inhibit APRIL and BAFF signalling, while zigakibart (BION-1301) and sibeprenlimab (VIS649) inhibit APRIL signalling only.

has been shown to regulate the development of plasma cells, which are specialized B cells that secrete large amounts of immunoglobulins. APRIL is produced by various immune cells, including macrophages, dendritic cells and activated T cells, and APRIL exerts its effects through the ligation of BCMA and TACI receptors (Fig. 2). BCMA is expressed by plasmablasts and plasma cells, and promotes plasma cell survival, while TACI is critical for T-cell-independent responses of B cells to type I and II antigens, negative regulation of the B-cell compartment and importantly, class-switch recombination of B cells.

Closely associated with the APRIL system is the B-cell-activating factor of the TNF family (BAFF) system. BAFF is also known as TNF ligand superfamily member 13B or B-lymphocyte stimulator (BLyS). BAFF can interact with the receptors BCMA and TACI but is the sole ligand for BAFF receptor (BAFF-R), also known as TNF receptor superfamily member 13C. BAFF-R is essential for both survival and maturation of immature B cells. Although APRIL and BAFF exhibit structural similarity (50% homology at the protein level) and overlapping receptor binding specificity, it is thought that the binding of APRIL and BAFF to the various receptors occur via distinct mechanisms and with differing affinity, and that the two ligands may therefore play different biological roles, in different phases of B cell regulation [25]. These subtle distinctions may explain possible differences in targeting APRIL, BAFF or both as a treatment strategy in associated diseases.

In addition to the general understanding of APRIL in B-cell regulation, the specific function of APRIL in IgA class switching was demonstrated in APRIL-deficient mice [26]. In APRIL$^{-/-}$ mice, serum IgA levels were significantly decreased and serum IgA antibody responses to mucosal antigen stimulation were impaired, while there was normal T- and B-lymphocyte development and normal T- and B-cell proliferation *in vitro*. Overall, APRIL is an important cytokine in the immune system in health, involved in regulating the maturation, differentiation and survival of B cells, and plays a specific role in IgA class switching.

APRIL has been implicated in the pathogenesis of several autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome and multiple sclerosis [24]. Serum APRIL levels have been shown to be elevated in these diseases [27–29], and high serum APRIL levels correlate with increased disease activity [30, 31]. It is postulated that APRIL can contribute to autoimmune diseases by breaking tolerance during B-cell development leading to activation and proliferation of autoreactive B cells resulting in the production of autoantibodies, and also by enhancing plasmablast survival. However, the direct role of dysregulated APRIL signalling in individual diseases and the relative contribution of APRIL to disease induction and/or progression remains to be clarified. Unsurprisingly, targeting APRIL in various autoimmune diseases has become an attractive potential therapeutic strategy [24].

## ROLE OF APRIL IN THE PATHOGENESIS AND PROGRESSION OF IGAN

The origin and mechanisms driving the production of Gd-IgA1, in particular the role of the mucosal immune system and B cell/plasma cell dysregulation, have been the subject of extensive study. It has long been observed that patients with IgAN develop episodic visible haematuria after an upper respiratory tract infection (termed synpharyngitic haematuria) [32], and that circulating and mesangial polymeric IgA1 have been observed to display a mucosal phenotype [33, 34]. These observations, coupled with an increase in polymeric IgA1 plasma cells in the bone marrow of patients with IgAN, which is believed to be due to mistrafficking of mucosally derived B cells, primed by cytokines such as APRIL, suggest dysregulation of the mucosal immune system is critical in the development of IgAN

[35]. Peripheral B-cell depletion using the monoclonal anti-CD20 antibody rituximab had no effect on serum levels of Gd-IgA1, its autoantibodies or proteinuria in IgAN [36]. Hence, significant attention has been directed towards the specific mechanisms promoting the production of Gd-IgA1 and the survival of mucosal-derived $IgA^+$ B cells/plasma cells. This has included study of the mediators that promote B-cell maturation and proliferation, the role of the APRIL axis in B-cell signalling, class-switching, IgA production and $IgA^+$ plasma cell survival. Given its pivotal role in B-cell activation and survival, elucidating the specific role of APRIL in IgAN, especially its role in Gd-IgA1 production, has been the focus of a number of animal and clinical studies.

## ANIMAL AND CLINICAL STUDIES OF THE ROLE OF APRIL IN IGAN

In a study of human tonsils, gene expression of APRIL was found to be elevated in tonsillar germinal centres of patients with IgAN and overexpression of APRIL in tonsillar germinal centres correlated with serum levels of Gd-IgA1 and disease severity in patients with IgAN [37]. The same investigators later demonstrated that, in an animal model of IgAN, toll-like receptor 9 activation increased gene expression and serum levels of APRIL, and that serum levels of APRIL were associated with over-production of Gd-IgA1, while siRNA knock-down of APRIL completely suppressed overproduction of Gd-IgA1 [38].

In a mouse model of IgAN, the administration of an anti-APRIL monoclonal antibody intraperitoneally significantly reduced albuminuria and tissue damage, combined with reduction in serum IgA levels and decreased deposition of mesangial IgA [39]. The investigators further showed that the decrease in serum IgA levels and mesangial IgA deposits were not associated with observable changes in the population of IgA-secreting plasmablasts or plasma cells in the bone marrow and spleen, suggesting that APRIL antagonism had influenced a specific IgA-producing B-cell population. Consistent with these findings, an earlier *in vitro* study had demonstrated that IgA-plasmablast differentiation was dependent on APRIL, whereas IgG-plasmablast differentiation was dependent on BAFF [40].

Similarly, it was shown in a separate study that a mouse anti-APRIL monoclonal antibody reduced pathogenic IgA immune complex formation and mesangial IgA deposition, with an associated reduction in kidney damage and loss of kidney function. In preclinical primate studies, treatment with sibeprenlimab (VIS649), a humanized IgG2 anti-APRIL monoclonal antibody, resulted in a dose-dependent reduction of serum IgA levels by up to 70% [41], supporting the role of APRIL in determining IgA production and its potential as a therapeutic target in IgAN.

In clinical studies it has been shown that APRIL (and BAFF, to a lesser extent) levels are elevated in the serum of patients with IgAN [42]. In these studies serum APRIL levels were elevated 3- to 20-fold above those of the controls, but only in a subset of patients, and were associated with age, serum creatinine and urine protein:creatinine ratio.

In a key study of 410 IgAN patients from Korea, the investigators demonstrated that, firstly, plasma APRIL levels in IgAN were significantly higher compared with healthy individuals and membranous nephropathy patients, and secondly, that kidney function and more importantly, subsequent risk of kidney failure in IgAN were correlated with tertiles of plasma APRIL level [43]. The investigators further demonstrated that exposure of IgAN patient B cells *in vitro* to recombinant human APRIL significantly increased the levels of secreted Gd-IgA1, while the total normalized IgA levels did not change, postulating that APRIL mediates its effects in IgAN development and/or progression through a relative increase in Gd-IgA1 levels.

Likewise, in another study of 166 Chinese IgAN patients, plasma APRIL levels were significantly higher in patients with IgAN than in healthy subjects. Elevated APRIL levels were significantly associated with higher levels of proteinuria and lower levels of eGFR at diagnosis, compared with patients with lower APRIL levels, and that plasma APRIL levels showed a strong positive correlation with Gd-IgA1 levels [44]. Interestingly, the investigators demonstrated that APRIL increased Gd-IgA1 production in lymphocytes from IgAN patients, but not from healthy subjects, suggesting that additional B-cell dysregulation in IgAN is necessary for APRIL to exert its effect.

Beside these key clinical studies, other smaller studies have further supported the role of APRIL in the pathogenesis and progression of IgAN or clarified additional pathways by which APRIL exerts its effect. In a single-centre study of 33 kidney transplant recipients, preliminary data showed that serum APRIL levels increased more in those patients who developed IgAN recurrence post–kidney transplant [16]. Beyond its role in B-cell dysregulation it has been suggested that APRIL may directly promote the proliferation of mesangial cells [45], enhance T-cell-independent immune responses in the mucosa [41, 46, 47], and play a direct role in IgA1 post-translational modification by regulating the expression of *O*-glycosyltransferases in B cells [41] .

## EVIDENCE FROM GENETIC STUDIES OF A ROLE FOR APRIL IN IGAN

GWAS have identified multiple susceptibility loci for IgAN, implicating independent involvement of the intestinal mucosal system, the adaptive and innate immune systems, and the alternative complement pathway. Significantly, a risk allele in the 17p23 *TNFSF13* locus which encodes APRIL has also been identified [48–50]. This susceptibility locus was first described in a study including a Han Chinese cohort of 4137 cases and 7734 controls. It was later determined that the minor risk allele rs3803800 (A) is estimated to confer an effect size of 20% and has an allele frequency of 22%, 28% and 79% in Europeans, Asians and Africans, respectively [51].

The susceptibility locus in 17p23 *TNFSF13*, in combination with other susceptibility genetic loci, are thought to influence IgA1 production and class switching, and dysregulated mucosal immune responses, all of which are central to the development and progression of IgAN. An interesting observation is that the risk variant in *TNFSF13* is associated with increased total IgA levels in IgAN patients but decreased levels in non-IgAN subjects [50, 52]. This observation is consistent with earlier studies reporting that the effects of APRIL on class switching are dependent on additional factors including the microenvironment cytokine milieu and as yet ill-defined B-cell changes [44, 53].

More recently, a GWAS in IgAN involving 10 146 biopsy-proven cases and 28 751 controls confirmed *TNFSF13* again as a susceptibility locus and also identified *TNFRSF13B* (encoding TACI), located on chromosome 17p11, as a new susceptibility locus [54]. The *TNFRSF13B* risk allele rs57382045 (A) has a minor allele frequency of 11% and 33% in controls of European and Asian ancestries, respectively. Importantly, the simultaneous identification of *TNFSF13* and *TNFRSF13B* as risk loci in IgAN, a cytokine ligand-receptor pair encoding for APRIL and TACI respectively, further supports a key role for the APRIL system in the development of IgAN. In addition, these genes were

also associated with serum IgA levels in a quantitative trait GWAS.

While the identification of susceptibility loci is supportive of a role of the APRIL system in IgAN, the precise role of these allelic variants at the various cellular and molecular level remain to be clarified. In a study involving subjects with multiple sclerosis and systemic lupus erythematosus, investigators demonstrated that the risk variant associated with *TNFSF13B* (GCTGT→A, in which A is the risk allele) increased the risk of autoimmunity due to the generation of a shorter *TNFSF13B* transcript that escaped microRNA inhibition, resulting in higher levels of soluble BAFF [55]. Additionally, the investigators further identified the population-level evolutionary selection advantage of the causal variant (resistance to malaria) that resulted in the present-day risk of autoimmunity. Identifying the functional consequences of risk variants in *TNFSF13* and *TNFRSF13B* in IgAN will strengthen the association between this pathway and disease development and possibly provide an explanation for the different population-level risk allele and disease frequencies. Nonetheless, the identification of genetic susceptibility loci involving a cytokine-receptor pair highlights the importance of this signalling pathway and the therapeutic potential for disrupting this pathway in IgAN [56].

Collectively, these observations provide compellingly evidence that APRIL contributes to the production of Gd-IgA1 in IgAN and supports the rationale for targeting APRIL. What remains unclear is the relative contribution of APRIL and BAFF in the pathogenesis of IgAN, and whether these cytokines have differing roles at different stages of the disease and in different patient subgroups [11]. Understanding the interaction between APRIL and BAFF in IgAN requires more investigation. What we can say is that there is an increasing body of evidence from genetic, animal and clinical studies supporting a role for APRIL in driving the production of pathogenic Gd-IgA1, and supports APRIL as a rational therapeutic target in IgAN.

## APRIL AS A THERAPEUTIC TARGET IN IGAN

Several novel experimental agents targeting the APRIL system and its related pathways are currently under investigation (Table 2).

### Atacicept

Atacicept is a human recombinant fusion protein of TACI and IgG1. It has the ability to inhibit APRIL signalling, leading to a decrease in B-cell numbers, and interfering with B-cell maturation, differentiation and effector functions [57, 58]. Notably, atacicept has the potential to inhibit both APRIL and BAFF, and it is not clear if this may result in differences in efficacy and/or safety, compared with agents targeting APRIL alone (sibeprenlimab or zigakibart, see below) or BAFF alone (blisibimod). In studies including patients with systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis, atacicept has been shown to be well tolerated, decrease serum immunoglobulin levels (including IgA) and impact on disease activity [59–64].

In a randomized, double-blind, placebo-controlled phase 2 study of 16 patients with IgAN and persistent proteinuria, the JANUS study (NCT02808429), atacicept was given weekly via the subcutaneous route for up to 72 weeks [65]. The study was terminated early due to slow recruitment but nevertheless, when compared against placebo, atacicept demonstrated an acceptable safety profile and treatment resulted in a dose-dependent reduction in immunoglobulin and Gd-IgA1 levels,

**Table 2: Ongoing or recently completed clinical trials of anti-APRIL therapies in IgAN.**

| Agent | Trial phase | Clinical trial name, number | Route of administration | Current status |
|---|---|---|---|---|
| Atacicept | II | JANUS, NCT02808429 | Weekly SC | Reported outcomes: reduction in Gd-IgA1 and proteinuria |
| | IIb | ORIGIN, NCT04716231 | Weekly SC | Completed recruitment; full results awaited |
| Telitacicept | II | NCT04291781 | 4-weekly SC | Reported outcomes: reduction in proteinuria |
| Zigakibart | I/II | ADU-CL-19, NCT03945318 | 2-weekly IV/2-weekly SC | Completed recruitment; full results awaited |
| Sibeprenlimab | II | EnVISion, NCT04287985 | 4-weekly IV | Completed recruitment; full results awaited |
| | III | VISionary, NCT05248646 | 4-weekly SC | Recruitment ongoing |
| | II/III | NCT05248659 | 4-weekly SC (single-arm, open-label) | By invitation, for subjects who completed phase II/III sibeprenlimab RCT studies |

IV, intravenous; SC, subcutaneous.

with improvement in proteinuria and stabilization of kidney function. In particular, the level of pathogenic Gd-IgA1 was reduced by up to 60% at Week 24, a magnitude of effect not previously demonstrated by other immunomodulatory agents, and *post hoc* analyses showed a correlation between the magnitude of Gd-IgA1 reduction and improvement in proteinuria. ORIGIN (NCT04716231), a larger ($n = 116$) and longer duration phase 2b study, which included a higher dose of atacicept (150 mg), has completed enrolment. Preliminary top-line results demonstrate a 33% mean reduction in proteinuria from baseline at Week 24, with available data showing a trend towards further reductions in proteinuria at Week 36 and stabilization of kidney function. Again, atacicept robustly reduced Gd-IgA1 levels from baseline through 24 weeks. The full publication of ORIGIN is keenly awaited, and a pivotal phase 3 study of atacicept in IgAN is expected.

### Telitacicept

Telitacicept is a soluble fusion protein composed of TACI and the fragment crystallizable (Fc) portion of IgG, which, like atacicept, can inhibit both APRIL and BAFF. Telitacicept has been approved in China for the treatment of patients with active systemic lupus erythematosus, based on previous studies [66–70]. In a phase 2 study of 44 patients with IgAN in China (NCT04291781), telitacicept, dosed once every 4 weeks for 24 weeks resulted in a dose-dependent reduction in proteinuria and stabilization of kidney function [71]. Telitacicept was well tolerated, and although immunoglobulin levels were decreased in patients receiving telitacicept, the levels of Gd-IgA1 have not been reported.

### Zigakibart

Zigakibart (BION-1301) is a humanized IgG4 monoclonal antibody that binds to APRIL. A phase 1/2 trial investigating zigakibart in patients with IgAN (NCT03945318) has completed recruitment and is currently in follow-up. Preliminary results suggest that zigakibart is well tolerated, and treatment results in reductions in serum levels of free APRIL, immunoglobulins, Gd-IgA1 and proteinuria [72–74]. Data available so far show that the reductions in IgA and Gd-IgA1 were maintained beyond 52 weeks of treatment, in conjunction with reduction in IgG to a lesser extent than IgA. Plans for a phase 3 study are underway, and publication of the phase 2 results are awaited.

### Sibeprenlimab

Sibeprenlimab (VIS649) is a humanized IgG2 monoclonal antibody that inhibits APRIL and is currently being evaluated in the VISionary phase 3 study. In a phase 1 study of 51 healthy volunteers (NCT03719443), sibeprenlimab was well tolerated and reversibly suppressed serum APRIL, immunoglobulins and Gd-IgA1 in a dose-dependent manner [71]. Results from the phase 2 EnVISion study (NCT04287985) similarly demonstrated reduction in Gd-IgA1 and IgA levels, in association with reduction in proteinuria [75]. A phase 3 study of sibeprenlimab in IgAN (NCT05248646), VISionary, is open and enrolling patients. Patients completing the phase 2 and 3 randomized controlled trials are being invited to enrol in an open-label extension study (NCT05248659). The publication of the phase 2 results is awaited (recently published).

As all of these agents are still in early phases of development it is difficult to draw any firm conclusions on any individual drug. However, what is striking is that there is a consistency of response in IgAN with all of these approaches confirming the therapeutic potential of B cell targeting through inhibition of APRIL and/or BAFF signalling in IgAN. We of course need to acknowledge that these studies are small and have relatively short-term follow-up, making it impossible to determine their longer-term impact on kidney function. These data will be delivered by the larger and longer duration phase 3 studies currently recruiting or in set-up.

## CONCLUSION

Treatments targeting disease-specific pathways in IgAN are urgently needed to improve outcomes in our patients. Evidence from genetic, animal and clinical studies support the pivotal role of APRIL in IgAN, through its effect on the production of pathogenic Gd-IgA1. It is attractive to consider that APRIL inhibition may offer a novel therapeutic strategy to specifically reduce the production of Gd-IgA1 and block the persistence of pathogenic $IgA^+$ plasma cells. Indeed, there are now several experimental agents targeting APRIL under study. Preliminary results are encouraging and phase 3 studies to better evaluate these treatment approaches are keenly awaited.

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## DATA AVAILABILITY STATEMENT

All data and results presented in this CKJ review is publicly available.

## CONFLICT OF INTEREST STATEMENT

SCY and JB are investigators of completed and ongoing clinical trials in IgAN, including experimental agents described in this review.

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