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New Insights into the Pathogenesis and Treatment Strategies in IgA Nephropathy

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Abstract
Background: Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide. It is defined by mesangial IgA deposition, with consequent mesangial cell proliferation, inflammation, and tubulointerstitial fibrosis. ***Summary:*** Approximately 30% of affected patients will progress to end-stage kidney disease within 20 years of diagnosis. Currently, there is no disease-specific treatment available and management recommendations are, in general, limited to optimization of lifestyle measures and use of renin-angiotensin-aldosterone system blockers. More recently, advances in the understanding of the pathogenesis of IgAN have informed the development of novel therapeutic strategies that are now being tested in clinical trials. These have focused on different areas that include modulating the production of poorly galactosylated IgA1, which is central to the development of IgAN, and inhibiting the downstream signaling pathways and complement activation that are triggered following mesangial IgA1 deposition. In this review, we will summarize important pathogenic mechanisms in IgAN and highlight important areas of interest where treatment strategies are being developed. ***Key messages:*** IgAN is a common form of primary glomerulonephritis for which there is no current approved specific therapy. Recent advances in the understanding of its pathogenesis have led to the development of novel therapies, with the hope that new treatment options will be available soon to treat this condition.

Introduction

Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis worldwide, with an estimated incidence of at least 2.5 per 100,000 per year in adults, and a higher frequency in East Asian countries [1]. The condition is characterized by IgA deposition in the glomerular mesangium, which initiates inflammatory cytokine release and complement activation, resulting in mesangial cell proliferation, extracellular matrix deposition, tubulointerstitial fibrosis, and, in approximately 30% of patients, end-stage kidney disease within 20 years of diagnosis. The exact mechanisms that result in IgA deposition are not completely understood; however, the frequent recurrence of glomerular IgA deposition after kidney transplantation

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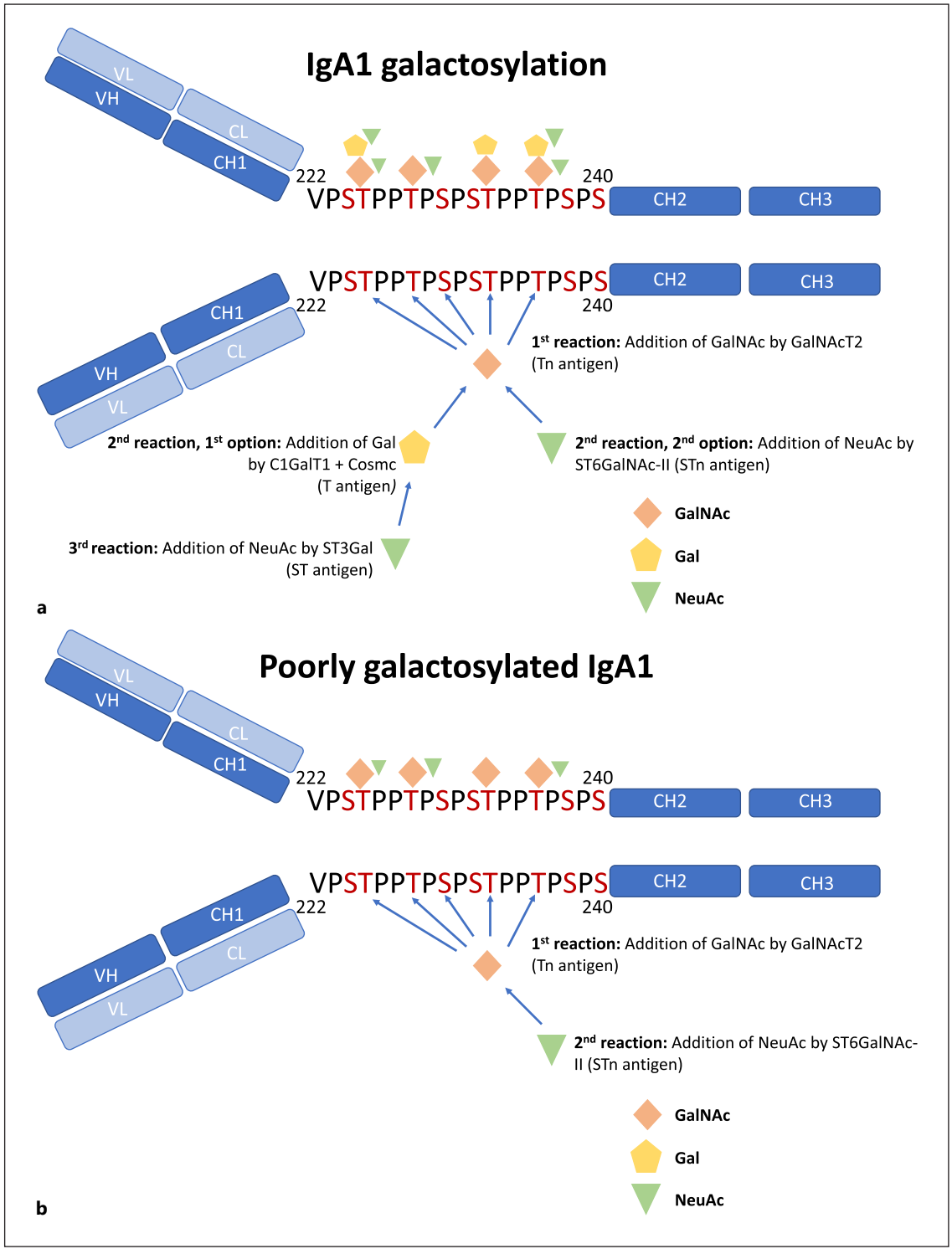
and reports of clearance of deposited IgA after transplantation of an affected kidney into a non-IgAN recipient indicate that the defect in IgAN is systemic rather than confined to the kidney [2, 3].

At present, there is no disease-specific treatment available for IgAN. Treatment recommendations are mainly limited to optimization of lifestyle measures, including strict blood pressure control, weight reduction, smoking



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cessation and cholesterol reduction, and use of renin-angiotensin-aldosterone system (RAAS) blockers. Current Kidney Disease: Improving Global Outcomes guidelines suggest the use of corticosteroids if these measures fail to reduce proteinuria [4]. However, their risk-benefit profile has been recently brought into question by 2 randomized controlled trials (RCTs), STOP-IgAN and TESTING [5, 6]. Due to the autoimmune basis of IgAN, a number of immunosuppressive agents commonly used in other glomerular diseases have been tested, including cyclophosphamide, rituximab, azathioprine, and mycophenolate, but there has been no consistent evidence to support the routine use of any of these agents [7].

It is now widely accepted that IgAN occurs due to multiple "hits": an increase in circulating "pathogenic" poorly *O*-galactosylated IgA1, production-specific IgG and IgA autoantibodies that recognize this form of IgA1, IgA1-immune complex formation, and their deposition in the glomerular mesangium, triggering renal damage [8]. In this review, we will summarize emerging information regarding the pathogenesis of IgAN and describe how this has informed the development of new therapeutic strategies with the aim of intervening at each of these stages.

IgA1 *O*-Galactosylation

In humans, IgA exists as 2 isoforms, IgA1 and IgA2, which in turn exist as monomers or polymers, and is found within mucosal and circulating compartments. IgA1 differs from IgA2 in that it contains an extended 18 amino acid hinge region, between the first and second constant domains of the α1 heavy chain (Fig. 1a). This is variably *O*-galactosylated by the addition of *O*-glycans chains containing terminal galactose to serine and threonine residues at specific positions. At mucosal surfaces, IgA1 is the most abundant immunoglobulin and plays an important role in the host defense against microbial invasion. The role of IgA within the circulation is unclear. IgA1, with its variably galactosylated hinge region, only exists in humans and higher primates, and therefore, drug development has been hindered by the lack of an accurate and easily reproducible rodent model.

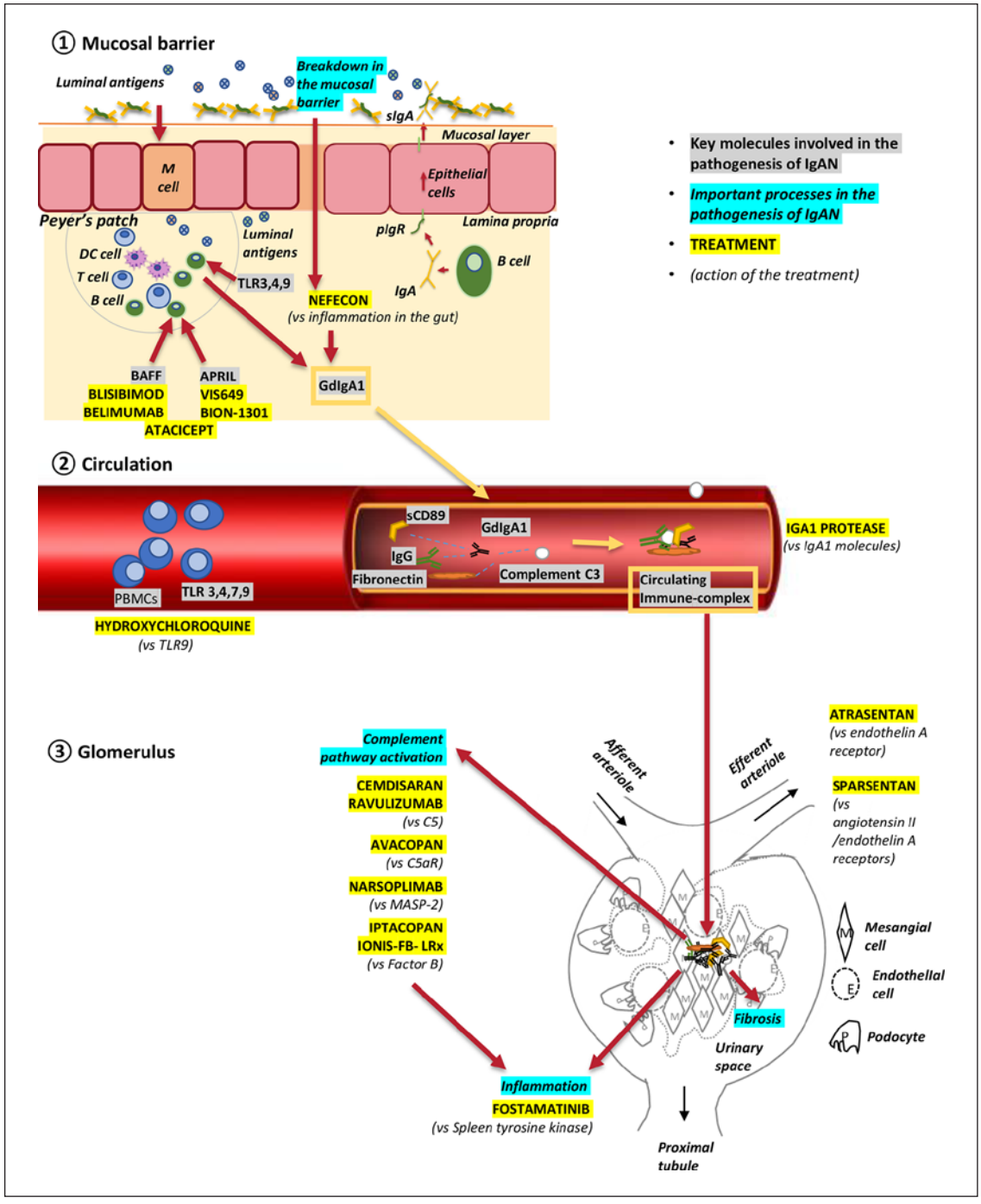
Serum IgA is composed mainly of the monomeric form, but in IgAN, there is an increase in circulating IgA1 that is polymeric and lacks terminal galactose residues in its hinge region (termed "poorly galactosylated IgA1," Fig. 1b) [9]. This form of IgA1 is usually most abundant within the mucosal compartment. In the circulation however, poorly galactosylated IgA1 may form immune complexes, with itself or with IgA and IgG antibodies directed against the hinge region. Lectin binding experiments, later confirmed by mass spectrometry, demonstrated that the IgA isolated from the mesangial deposits in IgAN is predominantly poorly galactosylated IgA1 [10, 11]. Serum levels of poorly galactosylated IgA1 have subsequently been demonstrated to correlate with renal prognosis [12].

Following mesangial deposition of IgA1, in susceptible individuals, a number of inflammatory and fibrotic processes are upregulated that lead to renal damage (Fig. 2). However, since raised serum levels of poorly galactosylated IgA1 may also be found in healthy individuals, notably in first degree relatives of patients with IgAN, and glomerular IgA1 deposition may occur in people who display no other features of clinically overt disease, additional factors to mesangial IgA1 deposition are likely to play a key role in the progression of IgAN [13].

O-Galactosylation of the IgA1-hinge region is influenced by a number of genetic and epigenetic factors, some of which have recently been characterized. Of note, core 1 beta 1, 3-galactosyltransferase (C1GalT1) is the enzyme responsible for attaching galactose to the IgA1

Fig. 1. IgA1 galactosylation. The IgA1 molecule contains a hinge region between the CH1 and CH2 domains, which is variably glycosylated. Six of the 9 possible glycosylation residues (indicated in red) can be elongated by the stepwise addition of monosaccharides, in *O*-linkage. **a** The addition of *O*-glycans starts by the binding of GalNAc residues to IgA1-hinge region serine or threonine residues by the GalNAcT2 enzyme, forming the Tn antigen. This can then be elongated by the addition of galactose residues by C1GALT1 and its chaperone Cosmc to form the T antigen, or alternatively the addition of NeuAc by ST6GalNac-II (STn antigen). The galactose residues can be extended by the addition of NeuAc by ST3Gal (ST antigen). IgA1 molecules may therefore possess a complex variety of glycosylation patterns. **b** Poorly galactosylated IgA1 molecules, found at increased levels in IgAN, miss the addition of galactose residues to the hinge region by the lower activity of C1GalT1/Cosmc enzymes and/or the addition of NeuAc residues to GalNAc by ST6GalNAc-II. P, proline; S, serine; T, threonine; GalNAc, N-acetylgalactosamine; Gal, galactose; NeuAc, neuraminic acid; CH1,2,3, constant heavy chain 1,2,3; VH, variable heavy chain; CL, constant light chain; VL, variable light chain; GalNAcT2, polypeptide N-acetylgalactosaminyltransferase 2; C1GalT1, core 1 beta 1, 3-galactosyltransferase; Cosmc, core 1 β3GalT-specific molecular chaperone; ST6GalNac-II, ST6 N-acetylgalactosaminide alpha-2,6-sialyltransferase 2, ST3Gal, alpha2,3-sialyltransferase.

hinge region. A common variant in the noncoding region of the *C1GALT1* gene has been identified, which is associated with increased levels of poorly galactosylated IgA1 [14]. This association with the noncoding area of the gene would be consistent with changes in the regulation of *C1GALT1* expression, possibly in specific microenvironments such as the mucosa, rather than a change in protein structure, which would affect all C1GALT1-expressing cell types. This finding is not restricted to those with IgAN but was also seen in healthy subjects and patients with membranous nephropathy, and in white and Chinese populations, implying that changes in IgA1 O-galactosylation are heritable and influenced by the *C1GALT1* gene. Interestingly, although IgAN has a higher preva-



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lence in Chinese than in white populations, levels of poorly galactosylated IgA1 were observed to be lower in Chinese IgAN patients than in white IgAN patients, and this corresponded with a lower frequency of the *C1GALT1* risk haplotype [15]. This raises important questions regarding whether other pathogenetic mechanisms act at differing levels in different populations and the relative importance of these mechanisms.

MicroRNAs (miRNAs) are short noncoding RNA molecules that modulate gene expression. Expression of the miRNA, miR-148b, has been shown to be increased in peripheral blood mononuclear cells (PBMCs) from patients with IgAN, and in vitro upregulation of miR-148b in PBMCs resulted in reduced expression of C1GalT1 and increased secretion of poorly galactosylated IgA1 [16]. A binding site for miR-148b within the *C1GALT1* gene has been identified [16].

A key area of interest in IgAN is therefore targeting these finely controlled processes (a further discussion of these can be found elsewhere [17]). Advances in technologies, for example, the ability to manipulate genes or miRNAs involved in IgA1 *O*-galactosylation, will likely be harnessed in the near future to design new therapies.

The Origin of Poorly *O*-Galactosylated IgA1 in IgAN

There has been long-standing interest in the links between IgAN and the mucosal immune system, with the observation that patients may experience episodes of visible hematuria that coincide with a respiratory or gastrointestinal infection. IgA, and in particular poorly galactosylated IgA1, is produced primarily at respiratory and gut mucosal surfaces, within the mucosa-associated lymphoid tissue (MALT). Important MALT sites implicated in the pathogenesis of IgAN are the tonsils and the gut (gut-associated lymphoid tissue [GALT]). The GALT produces the most IgA of all the MALT sites, and this is concentrated within specialized collections of lymphoid follicles called the Peyer's patches, in the distal ileum.

Growing evidence supports an important link between the gut mucosal system and IgAN. The incidence of certain gastrointestinal disorders, including inflammatory bowel disease and coeliac disease, is higher in patients with IgAN than in the general population [18]. Consistent with this, genome-wide association studies (GWAS) have identified multiple risk alleles for IgAN that are also associated with the immune response against intestinal pathogens, IgA synthesis within the gut, integrity of the intestinal epithelial barrier, and inflammatory bowel disease [19]. Two separate mouse models, a B-cell activating factor (BAFF)-overexpressing transgenic mouse and a humanized transgenic mouse that expresses human IgA1 and CD89, have been shown to be dependent on the presence of gut commensal flora to display an IgAN-renal phenotype [20, 21]. Intriguingly, a cross-sectional study demonstrated that patients with progressive IgAN may display differences in their gut microbiota profile [22]. Gut sensitivity to various mucosal antigens has also been reported in IgAN, although there is no clear evidence that any specific dietary modification has a clinically beneficial effect [23, 24].

Therapies directed towards the GALT have therefore become a key area of interest in IgAN. A targeted release formulation of budesonide (Nefecon) has been developed that is designed to specifically release the active drug at the distal ileum, targeting the Peyer's patches (Fig. 2). The NEFIGAN study was a Phase II RCT, studying the effects of Nefecon in IgAN (Table 1) [25]. A significant reduction in proteinuria and stabilization of kidney function was observed in those treated with 16 mg Nefecon daily for 9 months, compared to the placebo group where the

Fig. 2. A proposed pathogenesis for IgAN and potential therapeutic targets. 1. Mucosal barrier**:** Luminal antigens passing through the M cells of the epithelial barrier of the gut are recognized by TLR3, TLR4, and/or TLR9 on B cells in the Peyer's patches, leading to the release of poorly galactosylated IgA1 (also known as galactose-deficient IgA1 or GdIgA1). IgA produced by B cells in the mucosal barrier is bound by the pIgR. This process is crucial for the transcytosis of IgA molecules through the epithelial barrier and the release into the mucosal layer. Here, IgA molecules are present as sIgA, carrying the cleaved part of their pIgR, the secretory component. The production of IgA is sustained by the increase in BAFF and APRIL, key promoters of the maturation of B cells. In IgAN, a breakdown in the integrity of the intestinal mucosal layer may be responsible for the introduction of GdIgA1 from the mucosal layer. 2. Circulation: Raised levels of GdIgA1 are found in the serum in IgAN. GdIgA1 may originate from the gut mucosal barrier and/or from circulating PBMCs. The activation of TLRs on PBMCs could lead to increased production of GdIgA1. Circulating GdIgA1 forms complexes with other molecules, including IgG, sCD89, fibronectin, and complement C3. 3. Glomerulus: The IgA1-containing immune complexes deposit in the glomeruli, initiating complement pathway activation, inflammatory and fibrotic processes, and renal damage. Processes involved are highlighted in blue. Key molecules involved are highlighted in gray. New therapies in development are highlighted in yellow. PBMC, peripheral blood mononuclear cells; pIgR, polymeric immunoglobulin receptor; M, microfold; sCD89, soluble CD89.

Table 1. Ongoing or recently completed clinical trials of novel therapies in IgAN

Agent	Clinical trial design	Mechanism of action	Outcomes
Gut directed therapy			
TRF-budesonide (nefecon)	Phase III RCT (NefIgArd) – *ongoing* NCT03643965	Corticosteroid targeting B cells in GALT	
BAFF/APRIL directed therapies			
Atacicept	Phase II RCT – *terminated early (slow recruitment)* [29] NCT02808429 Phase II RCT (ORIGIN) – *ongoing* NCT04716231	Blocks BAFF and APRIL signaling	Reduction in GdIgA1 Reduction in proteinuria
Blisibimod	Phase II RCT (BRIGHT-SC) – *completed* NCT02062684	Selective BAFF inhibitor	Results awaited
BION-1301	Open-label Phase II trial – *ongoing* NCT03945318	Monoclonal Ab against APRIL	
VIS649	Phase II RCT (enVISion) – *ongoing* NCT04287985	Monoclonal Ab against APRIL	
B-cell directed therapies			
Rituximab	Phase II RCT – *completed* [30]	CD19/20^{+} B-cell depletion	No effect on proteinuria, eGFR, GdIgA1, or autoantibody production
Bortezomib	Phase II open-label pilot study – *completed* [31]	Proteasome inhibitor – depletes plasma cells	Reduction in proteinuria
TLR directed therapy			
Hydroxychloroquine	Phase II RCT – *completed* [37]	Inhibits TLR signaling	Reduction in proteinuria
Immunoreceptor signaling directed therapy			
Fostamatinib	Phase II RCT (SIGN) – *completed* [53]	Syk inhibitor	Nonsignificant reduction in proteinuria – full results awaited
Complement pathway inhibitors			
Iptacopan (LNP023)	Phase III RCT (APPLAUSE-IgAN) – *ongoing* NCT04578834	Factor B inhibitor – inhibits alternative pathway	
IONIS-FB-LRx	Open-label Phase II trial – *ongoing* NCT04014335	Factor B inhibitor – inhibits alternative pathway	
Cemdisiran	Phase II RCT – *ongoing* NCT03841448	Small-interfering RNA – inhibits C5 production	
Ravulizumab	Phase II RCT – *ongoing* NCT04564339	Monoclonal Ab against C5	
Avacopan	Open-label Phase II trial – *completed* [62]	C5a receptor blocker	Reduction in proteinuria
Narsoplimab (OMS-721)	Phase III RCT (ARTEMIS-IgAN) – *ongoing* NCT03608033	Monoclonal Ab against MASP-2 – inhibits lectin pathway	
Nonimmune modulators			
Sparsentan	Exploratory Phase II open-label mechanistic study (SPARTAN) – *ongoing* NCT04663204 Phase III RCT (PROTECT) – *ongoing* NCT03762850	Combined ARB and ETA-R blocker	
Atrasentan	Phase III RCT (ALIGN) – *ongoing* NCT04573478	ETA-R blocker	

Data from www.clinicaltrials.gov (accessed on 13 July 2021). TRF, targeted release formulation; RCT, randomized controlled trial; BAFF, B-cell activating factor; APRIL, a proliferation-inducing ligand; GdIgA1, galactose-deficient IgA1; Ab, antibody; MASP-2, mannose-binding protein-associated serine protease 2; ARB, angiotensin receptor blocker; GALT, gut-associated lymphoid tissue; TLR, toll-like receptor; Syk, spleen tyrosine kinase; ETA-R, endothelin-A receptor; eGFR, estimated glomerular filtration rate.

estimated glomerular filtration rate (eGFR) fell by an average of 4.7 mL/min/1.73 m^2. The Phase III NefIgArd trial, comparing treatment with Nefecon or placebo for 9 months in addition to maximum tolerated RAAS blockade, has recently completed recruitment and will examine efficacy over a 2-year follow-up period (ClinicalTrials.

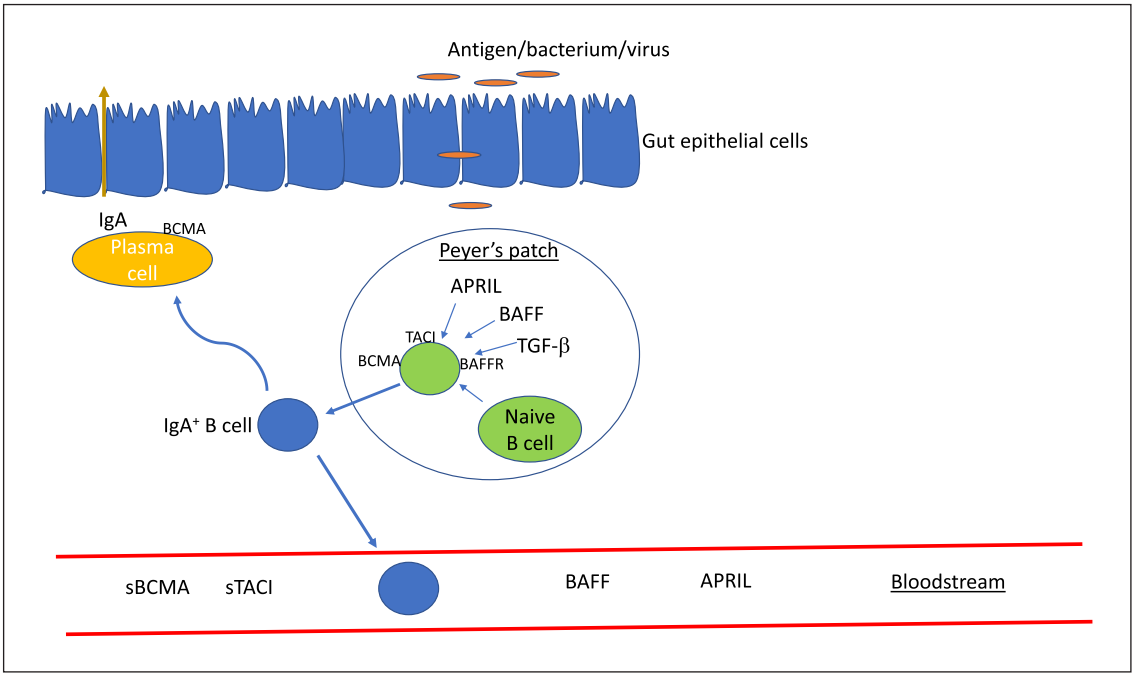


Fig. 3. Control of mucosal B-cell homeostasis by BAFF and APRIL. BAFF and APRIL are essential for the maturation and survival of GALT B cells, and IgA class switch recombination. BAFF and APRIL bind to the B-cell surface receptors TACI and BCMA at different stages in B-cell maturation, and BAFF also binds to BAFF-R. BAFF, B-cell activating factor; APRIL, a proliferating-inducing ligand; TACI, transmembrane activator and calcium modulator and cyclophilin-ligand interactor; BCMA, B-cell maturation antigen; BAFF-R, BAFF receptor; GALT, gut-associated lymphoid tissue.

gov identifier: NCT03643965). Investigating in detail the effects of targeting the GALT in this way may shed additional light on the importance of regulation of mucosal IgA1 production in IgAN. Potential differences in the composition of the gut microbiome in patients with IgAN compared to healthy subjects are intriguing and require further study with larger numbers of subjects, followed longitudinally, to assess whether this is a consistent finding, and if manipulation of the gut microbiome, for example, with probiotics, may be a future avenue for therapeutic intervention [26].

Modulation of Mucosal IgA Production in IgAN: The Role of BAFF and APRIL

Control of B-cell homeostasis in the Peyer's patches is a tightly regulated process controlled by BAFF, also called B lymphocyte activator, a proliferation-inducing ligand (APRIL), and their receptors, BAFF receptor (BAFF-R), B-cell maturation antigen, and transmembrane activator and calcium modulator and cyclophilin-ligand interactor (TACI) (Fig. 3) [17]. Raised levels of circulating BAFF and APRIL and an association between these cytokines and levels of circulating poorly galactosylated IgA1 suggest an important role for BAFF and APRIL in IgAN [17]. However, the data are not entirely consistent; it remains unclear whether BAFF or APRIL is the more relevant cytokine, or which is the dominant receptor subtype. The importance of the BAFF/APRIL system is supported by pre-clinical data in a BAFF-overexpressing transgenic mouse that displays a hyper-IgA syndrome and an IgAN-like renal phenotype, and the efficacy of an anti-APRIL antibody in the ddY mouse model of IgAN, in terms of reducing IgA deposition and proteinuria [20, 27, 28]. In addition, a GWAS has identified *TNFSF13* (which encodes APRIL) as a susceptibility locus for IgAN, and this risk variant is associated with higher levels of serum IgA in patients with IgAN [19].

Treatments inhibiting BAFF and APRIL signaling are being evaluated in clinical trials in IgAN. Atacicept is a fully humanized fusion protein containing the extracellular portion of TACI (a receptor for both BAFF and APRIL) that inhibits both signaling pathways. A 24-week

interim analysis of data from a Phase II RCT showed a dose-dependent reduction of circulating poorly O-galactosylated IgA1 and proteinuria in those treated with atacicept [29]. A Phase II trial of blisibimod, a selective inhibitor of BAFF, has been completed, and the full results are awaited (NCT02062684). Further clinical trials examining other BAFF and APRIL inhibitors are ongoing, including BION-1301, a humanized IgG4 monoclonal antibody that inhibits APRIL, and VIS649, a humanized IgG2 monoclonal antibody, also directed against APRIL (NCT03945318 and NCT04287985, respectively). IgG levels are known to fall after BAFF and/or APRIL inhibition. Whether these therapies have a specific effect on anti-IgA1 IgG autoantibodies is not yet clear but is an important area of interest.

In contrast to targeting BAFF and APRIL, depletion of $CD19/20^{+}$ B cells with rituximab has not been shown to be effective in a small open-label trial in IgAN [30]. Over a 1-year period, patients treated with rituximab had no improvement in proteinuria or kidney function compared to baseline or the control group, experienced more adverse events, and importantly had no reduction in serum levels of poorly galactosylated IgA1 or anti-IgA1 IgG autoantibodies, despite effective circulating B-cell depletion. This has led to the hypothesis that plasmablasts, plasma cells, or other tissue-resident B cells may play an important role in the production of poorly galactosylated IgA1 in IgAN. Therapies targeting other B-cell populations are currently being explored, and a pilot study of the proteasome inhibitor bortezomib recently demonstrated a reduction of proteinuria in 8 patients with IgAN [31].

Toll-Like Receptors

Control of BAFF and APRIL in the gut is, in part, modulated through Toll-like receptor (TLR) activation. TLRs mediate the host immune response to microbial stimuli, by recognition of pathogen-associated molecular patterns and danger-associated molecular patterns. TLRs are predominantly found on the surface of immune cells, but are also seen on other cell types including mucosal epithelial cells, where they face continuous microbiological stimuli. Activation of TLRs leads to the activation of a number of signaling cascades, resulting in production of interferons and release of pro-inflammatory cytokines that direct the adaptive immune response.

Links between a variety of TLRs, BAFF, and APRIL signaling and IgAN have been reported. Exposure of IgAN-prone ddY mice to the TLR9 ligand CpG-oligodeoxynucleotide increased the production of poorly galactosylated IgA, and exacerbated kidney injury, in a manner that was dependent on APRIL and IL-6 [32]. Stimulation of TLR9 also induced increased expression of APRIL by B cells isolated from tonsillar germinal centers in patients with IgAN, and clinically, increased APRIL expression by tonsillar germinal centers was linked with severity of proteinuria [33]. Similar to TLR9, TLR3 is activated by viral stimuli and may play a role in the pathogenesis of IgAN. In both patients with IgAN and in a rat model of IgAN, expression of TLR3 and BAFF was increased in blood and tonsillar samples [34]. Recently, increased expression of TLR7 was also shown in PBMCs from patients with IgAN, and this was associated with higher serum levels of poorly galactosylated IgA1 and markers of renal inflammation [35]. Renal expression of TLR4, TLR7, TLR8, and TLR9 has also been shown to be increased in IgAN, and associated with lower eGFR and increased proteinuria [36].

Hydroxychloroquine inhibits TLR9 and to a lesser extent TLR7 and TLR8 signaling. Given the proposed role of TLRs in IgAN, a RCT has been performed which demonstrated reduction of proteinuria in patients treated with hydroxychloroquine for 6 months [37]. However, this RCT was conducted in a small number of patients and was limited to Chinese patients, and therefore, the findings may not be generalizable. Hydroxychloroquine may be a potential therapeutic option and is known to be well tolerated and is of low cost, and therefore may have a large potential impact. Larger studies are required before any recommendation is possible, and in addition, a number of specific TLR antagonists are currently in development [38].

Circulating IgA1-Immune Complexes in IgAN

Elevated levels of circulating immune complexes containing poorly galactosylated IgA1 are commonly detected in patients with IgAN. In vitro, both polymeric IgA1 and IgG-IgA1-immune complexes, but not monomeric IgA1, have been shown to stimulate human mesangial cells, suggesting that components of the IgA1-immune complex play an important role in the pathogenesis of IgAN [39].

A key area of interest is the role of IgA and IgG antibodies with specificity for the poorly galactosylated IgA1 hinge region. IgG is variably found to be co-deposited with IgA in the mesangium in IgAN and when present has been linked to a worse prognosis [40]. In the serum, anti-IgA1 hinge region IgG antibodies were included in a panel of biomarkers reported to discriminate IgAN from other glomerular diseases [41]. Serum levels of both IgA1

and IgG anti-IgA1 hinge region antibodies have been associated with progression of IgAN [42]. IgG anti-IgA1 hinge region antibodies have also been detected within mesangial deposits in IgAN [43]. The ability of IgG to bind to poorly galactosylated IgA1 has been shown to be dependent on a somatic mutation causing an alanine to serine substitution in the CD3 domain of the variable region of the gene encoding for IgG [44].

One serum protein of interest that has been identified within IgA1-immune complexes in IgAN is the myeloid IgA receptor, CD89, which exists in both membrane-bound and soluble forms. There are conflicting reports regarding the clinical significance of IgA1-CD89 complexes in IgAN, and in particular, mesangial deposition of CD89 in IgAN has not been consistently demonstrated [45]. Glomerular deposition of Streptococcal M proteins in patients with IgAN and IgA vasculitis has been reported, again suggesting a link between mucosal infections and IgAN [46].A greater understanding of the constituents of circulating and mesangial IgA1-immune complexes may aid our understanding of the heterogeneity of clinical presentations in IgAN and potentially offer novel targets for therapeutic intervention.

Mesangial Deposition of IgA1 and Glomerular Injury

A number of in vitro studies have aimed to define the mechanisms by which deposition of IgA1-immune complexes leads to mesangial cell activation, proliferation, and release of pro-inflammatory and profibrotic mediators. Polymeric IgA1, poorly galactosylated IgA1, secretory IgA, and IgG-IgA1-immune complexes have all been reported to increase synthesis of pro-inflammatory cytokines by human mesangial cells [17]. The mechanisms by which mesangial cells recognize and respond to IgA1 are not completely understood. Binding of IgA-containing immune complexes to mesangial cell receptors is a possible critical pathogenic step and hence a potential therapeutic target. Therefore, intensive research efforts have been directed towards identifying candidate mesangial IgA1 receptors. Out of the known IgA receptors, only the transferrin receptor and Fcα/μR were previously demonstrated to be expressed by mesangial cells. More recently, a novel IgA receptor, β-1,4-galactosyltransferase 1, has been characterized and its expression by mesangial cells was increased in patients with IgAN [47].

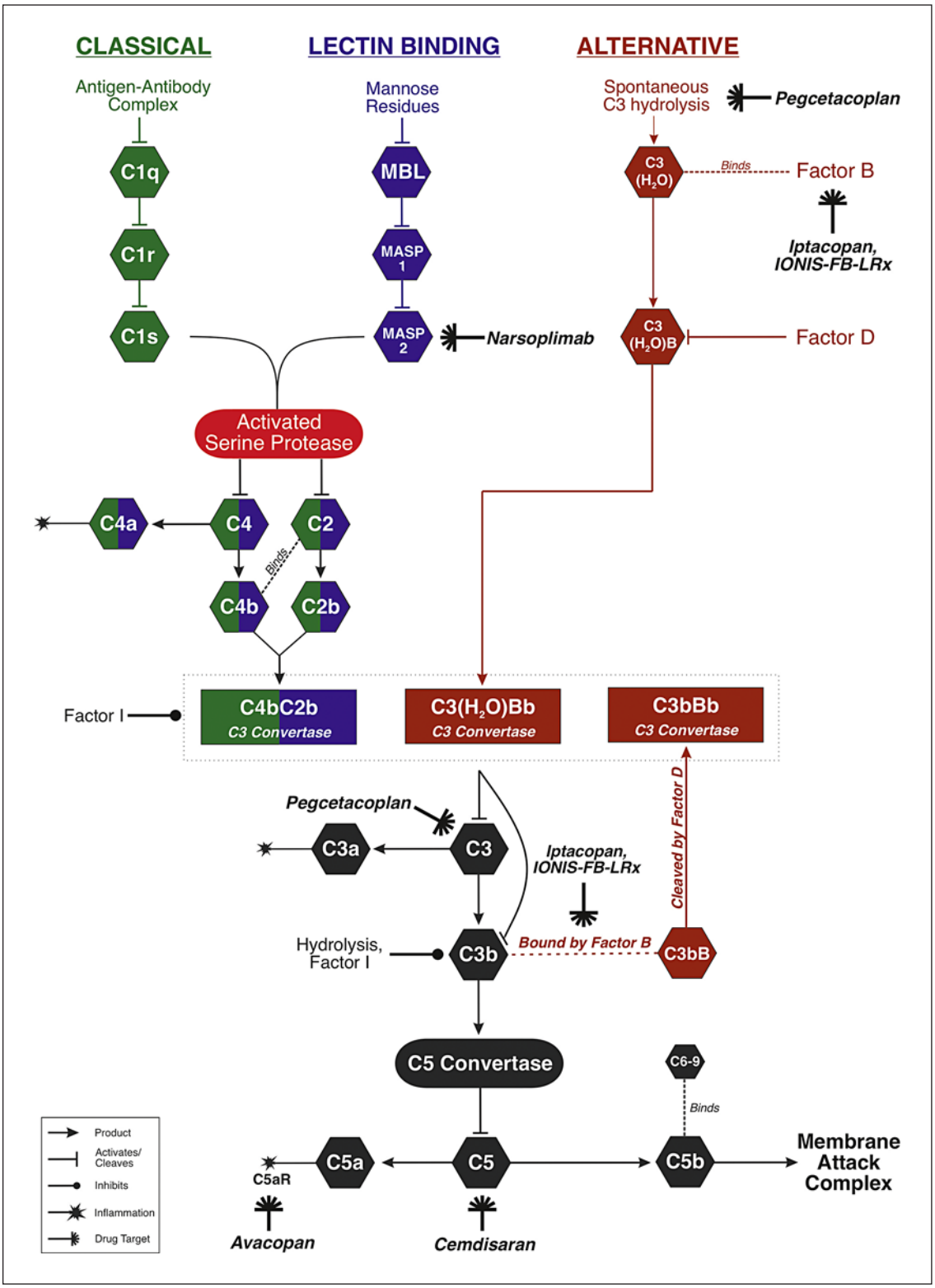
One treatment strategy that is being explored is the inhibition of downstream inflammatory pathways that may be activated following mesangial IgA1 deposition. Spleen tyrosine kinase (Syk) is a key protein involved in immunoreceptor signaling and activation of downstream pathways, including c-Jun and p38 MAPK [48]. Syk is expressed in different cell types, including myeloid and renal cells, and responds to the activation of B-cell receptors, Fc receptors, and IgA binding to beta 1,4 galactosyltransferase on the surface of human mesangial cells [47, 49]. Glomerular expression of Syk has been shown to be upregulated in IgAN and correlated with serum creatinine levels at the time of biopsy [50]. Inhibition of Syk signaling in vitro, either by siRNA knockdown or use of an active metabolite of the inhibitor fostamatinib, has been shown to block the inflammatory response of human mesangial cells following exposure to IgA1 from IgAN patients [51].

Syk inhibition is therefore a potentially attractive therapeutic strategy, especially as the Syk inhibitor fostamatinib has been shown to be well tolerated in large RCTs in chronic immune thrombocytopenia, and has been licensed for use in this condition [52]. A Phase II RCT of Syk inhibition in IgAN (SIGN: Syk inhibition in IgAN) has recently been completed. Preliminary results indicated a dose-dependent reduction in proteinuria in those treated with fostamatinib with a baseline urine PCR >1,000 mg/g, although this did not reach statistical significance [53]. The full results from this trial are awaited.

Complement Pathway Activation and IgAN

The complement system is a critically controlled trio of pathways composed of multiple heat-labile proteins, which provide an important link between the innate and adaptive immune systems. The 3 pathways, classical, alternative, and lectin, are differentially triggered but converge at the point of activating complement component 3 (C3) by the formation of pathway-specific C3 convertases. C3 activation ultimately results in the production of anaphylatoxins (C3a and C5a), leading to the recruitment of inflammatory mediators, and formation of the membrane attack complex, resulting in cell lysis (Fig. 4). Complement activation has been recognized to play an important role in several glomerular diseases, including atypical hemolytic uremic syndrome, C3 glomerulopathy, dense deposit disease, lupus nephritis, ANCA-associated vasculitis, and membranous nephropathy [54, 55].

C3 is co-deposited with mesangial IgA1 in the majority of patients with IgAN, and the near ubiquitous absence of C1q implies that in IgAN, alternative and/or lectin, but not classical, pathways are activated. Detection of



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alternative pathway components in renal biopsies, serum, and urine from IgAN patients has all been associated with worse renal outcome [56]. Lectin pathway activation can be demonstrated in a subgroup of patients with IgAN. In 2 independent IgAN cohorts, glomerular deposition of lectin pathway components was detected in approximately 25% of cases and was associated with worse disease severity [57, 58].

The origin of mesangial C3 deposits in IgAN has not been established, and potential sources include the circulation, either as a component of circulating IgA immune complexes or in situ fixation triggered following IgA immune complex deposition, and/or local production by resident mesangial cells or infiltrating immune cells [56]. Circulating C3 activation fragments can be detected in around half of patients with IgAN [56]. The ratio of serum IgA to C3 (IgA/C3) has been reported as a biomarker for diagnosis and progression of IgAN [59]. More recently, the ratio of poorly galactosylated IgA1 to C3 was reported to be predictive of progressive renal decline in IgAN, and this was independent of clinical and histological characteristics [60]. These reports are confined to cohorts from Asia, and further studies are needed to see whether these changes are also seen in other patient cohorts.

Two separate GWAS reported an association between the *CFH/CFHR* locus and IgAN. Deletion of complement factor-H-related protein-1 and protein-3 was shown to be protective against the risk of developing IgAN. Complement factor-H-related protein-1 and complement factor-H-related protein-1 compete with the binding of factor H to C3, and their deletion results in uninhibited factor H-C3 binding, and downregulation of the alternative pathway.

The increasing number of targeted complement pathway inhibitors has led to a great deal of interest in complement-directed therapies in IgAN. Initial case reports of C5 inhibition using eculizumab reported temporary slowing of renal decline in IgAN with rapidly progressive disease providing proof of concept for further evaluation of complement inhibition in IgAN [56]. A number of ongoing trials are evaluating drugs that target the alternative, lectin, and terminal complement pathways. Iptacopan (LNP023) is an oral selective factor B inhibitor that targets alternative pathway activation. A Phase III RCT is currently being conducted (NCT04578834), and this agent is also being studied in other conditions including membranous nephropathy, C3 glomerulopathy, atypical HUS, and paroxysmal nocturnal hemoglobinuria. IONIS-FB-LRx is an antisense inhibitor directed against Factor B mRNA, and its safety and efficacy are also being tested in patients with IgAN in a small single-arm open-label study (NCT04014335). Cemdisiran is an RNA interfering therapeutic agent that blocks hepatic production of C5, and a Phase II RCT is underway to investigate its effects in IgAN (NCT03841448). C5 is also being targeted in a Phase II study of the long-acting C5 inhibitor ravulizumab (NCT04564339). The C5a receptor can be specifically targeted by the oral small molecule inhibitor Avacopan (CCX168), which has been shown to be safe and effective as part of treatment for ANCA-associated vasculitis in a Phase III trial [61]. Results from an open-label Phase II trial in IgAN have been presented, which demonstrated a reduction in proteinuria by 12 weeks, in 6 out of 7 patients tested [62]. Narsoplimab (OMS-721) is a human monoclonal antibody that targets mannose-binding protein-associated serine protease 2 (MASP-2), a

Fig. 4. The complement system and therapeutics. The complement system can be activated by 3 arms. *The classical pathway* (*green*) is activated by antigen-antibody complexes, which bind C1q inducing a conformational change to permits the associated C1r to cleave C1s into an activated serine protease. C1s subsequently cleaves C4 to produce C4a, a strong inflammatory mediator, and C4b. C4b binds C2 permitting it to be cleaved by the serine protease, producing C2b. C4b and C2b bind to produce a C3 convertase. *The lectin binding pathway* (*purple*) is activated by mannose moieties commonly found on microbial surfaces, but also on poorly *O*-galactosylated IgA1. These moieties are bound by a MBL, which activates MASP-1 and MASP-2, which are analogous to C1r and C1s of the classical pathway. MASP-2 activation leads to C4bC2b production as detailed above. MASP-2 can be therapeutically inhibited by narsoplimab**.** *The alternative pathway* (*red*) is a constantly activated pathway, triggered by the hydrolysis of C3 (inhibited by Pegcetacoplan) thioester bonds. C3(H_20) is bound by Factor B, which renders the complex susceptible to cleavage by Factor D. This produces the C3 convertase C3(H_20)Bb. Factor B can be therapeutically inhibited by Iptacopan or IONIS-FB-LRx. *The common pathway* (*black*) is activated by any of the C3 convertases, which cleave C3 (inhibited by Pegcetacoplan) to C3a, an inflammatory mediator, and C3b. C3b is further acted upon by the C3 convertases to produce a C5 convertase, which cleaves C5 (can be inhibited by Cemdisiran) to produce C5a, a potent inflammatory mediator (its receptor can be inhibited by Avacopan) and C5b. C5b is serially bound by C5, C6, C7, C8, and C9 to form the MAC, which is capable of cell lysis. C3b can also be bound by Factor B of the alternative pathway to form C3bB, which can be cleaved by Factor D to produce the C3 convertase C3bBb. C3b activity is regulated by hydrolysis and Factor I, which inhibit its activity. MASP-2, mannose-binding protein-associated serine protease 2; MAC, membrane attack complex; MBL, mannose-binding lectin.

critical effector enzyme of the lectin pathway. A case report demonstrated stabilization of renal function in IgA vasculitis [63], and a staged Phase II study demonstrated that narsoplimab treatment was well-tolerated and reduced proteinuria in high-risk patients with IgAN, who had proteinuria >1 g/day [64]. A Phase III RCT of narsoplimab in IgAN is currently open to recruitment (NCT03608033).

Nonimmune Modulators

Sparsentan is a first-in-class combined angiotensin receptor blocker (ARB) and endothelin-A receptor (ETA-R) antagonist, which has both ARB and podocyte-protective effects as well as a number of other putative anti-fibrogenic, anti-inflammatory, and antioxidant actions and has shown promising results in terms of proteinuria reduction in a Phase II study in FSGS [65]. Sparsentan is currently being tested in IgAN in the Phase III PROTECT RCT and in a separate exploratory mechanistic sub-study (SPARTAN) (NCT03762850 and NCT04663204). A separate Phase III trial of the ETA-R antagonist, atrasentan, is also being conducted (ALIGN) (NCT04573478).

The sodium-glucose cotransporter 2 inhibitors (SGLT2i) are a novel class of medications that have recently been introduced for the treatment of diabetes mellitus. These work by enhancing glycosuria by blocking the proximal tubular SGLT2 cotransporter and inhibiting the entry of glucose into the proximal tubular cells. It has become apparent that these medications also provide significant renal and cardiovascular benefits that are independent of their anti-glycemic effects. The DAPA-CKD trial randomized 4,304 participants with eGFR between 25 and 75 mL/min/1.73 m^2, with or without type 2 diabetes mellitus, and was stopped early due to efficacy. Over a median of 2.4 years, there was a significant reduction in those reaching a primary outcome event of a sustained decrease in eGFR of at least 50%, end-stage kidney disease, or death from a renal or cardiovascular cause in those taking dapagliflozin rather than placebo [66]. A prespecified analysis of 270 participants with IgAN included in this trial again demonstrated a reduction in the primary outcome in those taking dapagliflozin, and also reductions in eGFR decline and albuminuria [67]. It should be noted that around 14% of these patients had coexistent diabetes mellitus and that not all patients had a biopsy-proven diagnosis of IgAN. Importantly, there was no run-in period in this trial where RAAS blockade was maximized, and therefore, it is possible that some patients could have responded to this measure alone, and ideally, a dedicated trial in IgAN incorporating this would allay these concerns [68]. The EMPA-KIDNEY trial, currently underway, will provide additional data regarding the additional effect of sodium-glucose cotransporter 2 inhibitors in CKD compared to conventional therapies [69].

Future Areas of Interest

To date, no treatment directly targets the circulating IgA1-immune complexes that are seen in IgAN. One potential area of interest is the IgA1-specific proteases. These are produced by several bacterial species, including *S. pneumoniae, N. meningitidis, N. gonorrhoeae,* and *H. influenzae*, and specifically cleave the IgA1-hinge region, so do not affect IgA2. The use of an IgA1 protease was tested in the α1KI-CD89 Tg mouse model of IgAN and resulted in reduced mesangial IgA deposits and hematuria [70]. In studies with BALB/c mice and in vitro tests, a consistent reduction of IgA1-IgG immune complexes has been observed [71]. The long-term safety and efficacy of this approach in humans have not yet been established. However, a similar approach is being tested with the use of the endopeptidase IdeS (immunoglobulin G degrading enzyme of *Streptococcus pyogenes*; Imlifidase), which rapidly cleaves all human IgG subclasses. Successful pilot studies have been carried out in highly sensitized patients undergoing renal transplantation to reduce donor-specific antibodies, and in anti-GBM disease, providing proof of concept that this treatment strategy may be effective in the treatment of autoimmune kidney disease [72, 73].

Despite the increased interest in performing clinical trials in IgAN, there remain important unmet needs. These include that the vast majority of clinical trials have not included patients with an eGFR <30 mL/min/1.73 m^2. Recurrence of IgAN after renal transplantation has also not been widely studied. Finally, patients with IgA vasculitis have largely been excluded from clinical trials, despite many aspects of its pathogenesis being similar to IgAN.

Conclusion

Important advances have been made in the last decade in our understanding of the molecular mechanisms involved in the pathogenesis of IgAN. Deeper knowledge of the pathways involved has led to a resurgence of interest

in developing new treatment strategies in IgAN, and in the number of Phase II and Phase III clinical trials evaluating new therapies. It is hopeful that within the next few years we will have the first approved treatment for IgAN and that this will be the first of many.

Many questions, however, continue to be unanswered, for example, the precise mechanism by which IgA deposits and leads to a response from mesangial cells, why IgAN causes progressive disease in certain patients and not others and the basis for the reported variations in disease severity and natural history between geographical areas. With the heterogeneity in presentation and outcomes, it has been suggested that IgAN may not represent a single disease and that mesangial IgA deposition is the final common endpoint for a range of disparate immunologically driven pathological pathways. Dissecting these different pathways will hopefully lead to the delivery of novel diagnostic and prognostic biomarkers, and the ability to individualize treatment to specific dysregulated pathways in patients with IgAN.

Conflict of Interest Statement

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