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Review

Recurrent Immunoglobulin A Nephropathy after Kidney Transplant—An Updated Review

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Abstract: Immunoglobulin A nephropathy (IgAN) is the commonest glomerulonephritis worldwide, a category that represents the third most frequent cause of end-stage kidney disease (ESKD) in the United States. Kidney transplantation remains the optimal treatment of ESKD, and yet the prospects of IgAN recurrence post-transplant dampens the enthusiasm for living kidney donation in some instances, in addition to limiting the longevity of the kidney allograft. Moreover, the lack of a standardized method for detecting IgAN recurrence, since not all centers perform protocol allograft biopsies, has led to an underestimation of the extent of the issue. The pathogenesis of de novo IgAN remains conjectural, let alone the pathways for recurrent disease, but is increasingly recognized as a multi-hit injury mechanism. Identification of recurrent disease rests mainly on clinical symptoms and signs (e.g., hematuria, proteinuria) and could only be definitively proven with histologic evidence which is invasive and prone to sampling error. Treatment had relied mainly on nonspecific goals of proteinuria reduction, and in some cases, immunosuppression for active, crescentic disease. More recently, newer targets have the potential to widen the armamentarium for directed therapies, with more studies on the horizon. This review article provides an update on recurrent IgAN post-transplant.

Keywords: IgA nephropathy; kidney transplantation; recurrent glomerulonephritis; immunosuppression; deficiently glycosylated IgA1

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1. Introduction

IgA nephropathy (IgAN) is caused by the deposition of deficiently glycosylated IgA1 (Gd-IgA1) in the renal parenchyma, leading to hematuria, proteinuria, and eventual renal function decline. Worldwide, it is the most common form of glomerulonephritis, with a population incidence of at least 2.5/100,000 [1]. More importantly, the burden of disease is highest in East Asian countries compared to North America and Europe, and exceedingly rare on the African continent. This geo-spatial variation is recently found to parallel that of inheritance patterns for genetic risk alleles, especially as it relates to local variations in pathogens, particularly of helminthic diversity [2]. While post-kidney transplant outcomes for patients with IgAN are exceedingly good, the risk of recurrence has been reported as 13–60% [3] depending on whether protocol or only for-cause biopsies are practiced. Furthermore, graft loss rates from recurrence at 10 years approximate 10% based on a large registry report with a substantial number of IgAN cases [4]. It represented the third most common cause of allograft loss, after chronic rejection and death with a functional allograft. Furthermore, those with recurrent glomerular diseases post-transplant had a

worse death-censored and overall graft survival than those without it (hazard ratio 3.58 and 4.06, respectively) [5]. A main predictor of IgA recurrence is the duration since transplant, where incidence increases with longer duration of follow-up [6].

Despite its prevalence and impact on long term allograft survival, treatment options have largely been limited. Up until recently, therapies have remained non-specific, targeted only at reducing proteinuria with inhibition of the renin–angiotensin–angiotensinogen system (RAAS) and immunosuppression (e.g., corticosteroids, calcineurin inhibitors, alkylating agents) for crescentic glomerulonephritis and acute flares. In the past few years, new treatments that target the gut-associated lymphoid tissue (GALT) [7] along with an agent that dually blocks the action of two mediators of renal disease progression (endothelin A and angiotensin II type 1) at their receptors [8] have been approved for use under the accelerated approval pathway. In addition, there are multiple other pharmaceutical agents being studied currently, focused on targets as wide ranging as B cell survival factors and the alternative pathway of the complement system.

2. Epidemiology

2.1. Native Disease

Subclinical disease from IgAN may never be detected but can come up incidentally during routine medical urinary tests or employment screenings [1]. Among those diagnosed with IgAN, around 20–30% of patients will eventually develop ESKD [6,9]. IgAN is the most prevalent form of glomerulonephritis in the world, although its true incidence is likely under-represented due to the lack of population-wide biopsy databases [10]. In a Japanese study (446 living and 64 deceased donors), time zero allograft biopsies were examined and found IgA deposition in 16% of cases [11]. Based on limited population-based studies in the USA, the annual incidence of biopsy-proven IgAN is ~1/100,000 persons, giving a life-time risk of 1 in 1400 [12]. There appears to be ethnic differences, with the highest incidence among Native Americans and lowest among non-Hispanic Whites in New Mexico [13]. The burden of disease is highest in East Asian countries compared to North America and Europe, and exceedingly rare on the African continent. This geo-spatial variation is recently found to parallel that of inheritance patterns for genetic risk alleles (see below), especially as it relates to local variations in pathogens, particularly of helminthic diversity [2].

2.2. Recurrent Disease Post-Renal Transplant

Current United States Renal Data System statistics demonstrated that although IgAN is a less common cause of ESKD than diabetes mellitus (DM), patients with IgAN experience higher rates of transplantation. This is likely due to the fact patients with IgAN generally have less comorbidities and reach ESKD at a younger age and may get earlier referral for transplant evaluation [14,15]. Recurrent glomerular disease after transplant represents the third most common cause of allograft failure, with IgAN being the most prevalent glomerular condition. IgAN recurrence after transplantation is common and has been reported to occur in up to 60% of patients [9]. Recurrence rates vary widely depending on the types of biopsies being performed, with IgAN recurring at a much higher frequency in protocol biopsy studies.

Immunosuppressive regimen may play a part in the risk of IgAN recurrence. Use of steroids for maintenance immunosuppression has been shown to be protective [16], an area that is explored later in the Treatment section. Among 116 renal transplant recipients, 10-yr cumulative incidence of IgAN recurrence was 9% among those who received anti-thymocyte globulin (ATG, most of which was rabbit derived) as induction, compared to 41% in those without induction (p = 0.001) [17]. Those receiving an anti-CD25 monoclonal antibody as induction at 5 years had a 41% cumulative incidence of IgAN recurrence. In multivariate Cox regression analysis, ATG remained protective with an 80% recurrence risk reduction (RR 0.20). In terms of maintenance immunosuppression, Ortiz et al. found that cyclosporine use was associated with lower recurrence rates [18]. In contrast, Mulay et al. found no influence of immunosuppressive regimen on the rates of graft failure due to

recurrent IgAN (tacrolimus vs. cyclosporine, azathioprine vs. MMF) [19]. The jury remains out on that question.

Risk factors for recurrent IgAN can be broken into three categories. Recipient-related risks include higher serum IgA levels at the time of transplant, younger age at transplantation, rapid progression of initial IgAN, and the degree of proteinuria [6,20,21]. Transplant associated risks include increased length of time after transplant and the type of induction immunosuppression used [6,17] as discussed above. Donor-related factors that could potentially increase recurrence risk include the use of a living donor, zero HLA mismatched kidneys (compared to those with 1 or more mismatches) and specific HLA haplotypes [22]. Table 1 Summarized these findings.

Table 1. Risks Factors for Recurrent IgA Nephropathy.

Recipient Related Risk Factors		**Donor Related Risk Factors**		**Transplant Associated Risk Factors**	
Higher Serum IgA level at the time of transplant	↑	Living Donor Transplantation	↑	Increasing Time After Transplant	↑
Younger Age at Transplantation	↑	Zero HLA Mismatched Kidney Allografts	↑	Use of Steroid Maintenance Immunosuppression	↓
Rapid Progression of Initial IgA to ESKD	↑	Specific HLA types * (B12, B35 DR4)	↑		
Higher Degree of Proteinuria	↑				

↑ Increased Risk ↓ Decreased Risk. * in some studies HLA type has been associated with increased risk.

3. Pathogenesis

The pathogenesis of native kidney IgAN involves a complex interplay of both genetic susceptibility with immunologic factors as well as host factors. Like native IgAN, there are multiple different mechanisms of graft injury in recurrent disease.

IgAN occurs in patients who have a predisposition to form poorly glycosylated IgA [23]. Typically, in native kidney disease, a respiratory or gastrointestinal illness will trigger a dysregulated immune reaction that leads to the production of antiglycan antibodies of either IgG or IgA subtypes. These antibodies bind poorly to glycosylated IgA1 which circulates in the serum and gets deposited in the mesangium. In the post-transplant setting, there are potentially modulating and protective factors which can influence the course of disease. Certain immunosuppressive regimens can potentially decrease the risk of recurrence [16,17]. As noted earlier, high levels of poorly glycosylated IgA1 pretransplant can increase the risk of recurrence post-transplant [24].

Complement activation has been shown to play a large role in glomerular injury in IgAN. The alternative pathway involvement is evidenced by C3 deposition seen in IgAN along with increased plasma concentration of C3b and C3d which are markers of C3 activation [25,26]. Evidence of lectin pathway involvement in IgAN is noted for the frequent glomerular deposition of their degradation products such as C4d and MBL (mannan-binding lectin) [27]. It is worth noting that presence of C4d on cells of peritubular capillaries and medullary vasa recta are used to help diagnose antibody mediated rejection in kidney transplant allografts [28], potentially implicating a common pathway in both processes when considering therapeutic targets. The classical pathway of the complement system has not shown pathogenetic involvement as C1q deposition (an activation by-product) is commonly absent in IgAN [29].

There has been growing evidence for the role of endothelin-1 (ET-1, a vasoconstrictor peptide) in progressive kidney disease, demonstrated by its robust association with mesangial proliferation and podocyte injury [30]. On renal biopsies stained for localization of ET-1 and endothelin receptor type B (ET-RB) protein along with their respective mRNA expression in patients with IgAN, it was shown that expression levels correlated with the degree of proteinuria [31]. Furthermore, those patients receiving angiotensin-converting enzyme inhibitors (ACEi) with declining proteinuria tracked closely with decreasing levels of mRNA expression of ET-1 and ET-RB in proximal tubular epithelial and glomerular cells.

B cell activation factor (BAFF) and anti-proliferation-inducing ligand (APRIL) are part of the tumor necrosis factor superfamily which has an important role in B-cell proliferation leading to antibody production including excessive IgA in native kidney disease [32,33]. Animal studies have previously shown that over expression of BAFF leads to IgAN-like disease suggesting possible linkage [34]. BAFF level post-transplant may have a potential role as a biomarker in predicting kidney allograft rejection [35], and in the case of recurrent IgAN disease, treatment with an anti-BAFF agent could potentially also ameliorate the risks of an immunologic event. Animal studies using anti-APRIL monoclonal antibody has shown promising potential therapeutic benefits including the suppression of serum IgA levels, circulating immune complexes, intra-renal deposition if IgA, IgG and C3 in addition to lowering of proteinuria in a murine and non-human primate model [36]. Along these lines, long-lived plasma cells that have expanded endoplasmic reticulum, and capable of synthesizing antibodies on a perpetual basis, maybe an important source of Gd-IgA1 and anti-Gd-IgA1 antibodies that drive initiation and progression of IgAN [37]. Moreover, plasma cells do not possess CD20 which is a common cell surface marker on mature B cells and would explain why generic anti-CD20 therapies such as rituximab have not been shown to be effective in curbing IgAN. Instead, plasma cells exhibit a high expression of CD38, which is seen in greater abundance among IgAN patients vs. control [38].

Spleen tyrosine kinase (Syk) is an intracellular protein involved in cell signaling [39]. It is expressed in many cell types including B lymphocytes which promotes the cascade that eventually leads to production of inflammatory and pro-fibrogenic mediators contributing to mesangial and tubular injury of IgAN in native kidneys [40,41]. The use of Syk inhibitors was shown to reduce proteinuria, glomerular macrophages and Cd8+ cells and proinflammatory cytokine infiltration and histological injury in a mouse model [42]. More importantly, it improved renal function and decreased renal crescents even when given after the onset of glomerulonephritis. In a study of kidney transplant of highly sensitized animals, the use of Syk inhibitor showed a potential role in attenuating the risk of antibody mediated rejection in rat kidney transplantation, again bringing up the salutary effects of an IgAN-directed therapy on transplant rejection [43]. However, the roles of BAFF, APRIL, and Syk in recurrent IgAN post kidney transplantation remain unclear, as most studies to date have focused on IgAN in native kidneys.

4. Genetic Basis of IgAN

As discussed earlier, the pathogenesis of recurrent IgAN appears to follow a multi-hit hypothesis, in individuals primed with a genetic predisposition, triggered by an environmental exposure leading to immune dysregulation and eventual renal injury. The genetic basis for renal diseases has seen renewed interest recently, starting with a pivotal study showing how exome sequencing could potentially identify a monogenic etiology in up to 10% of individuals with chronic kidney disease (CKD) [24]. In complex, polygenic conditions such as IgAN, genome-wide association studies (GWAS) have proven invaluable in identifying susceptibility loci in its pathogenesis. This method is capable of interrogating common single nucleotide variants (SNVs) in the millions through the aid of imputation.

From an epidemiologic perspective, GWAS have identified a link between susceptibility loci involved in determining intestinal mucosal barrier integrity and the geospatial distribution of IgAN (most common among East Asians and Northern Europeans and rare on the African continent). Its prevalence closely parallels the variation in local pathogens, suggesting a multi-locus adaptation to helminthic diversity [2]. GWAS have also implicated risk loci and candidate genes involved in antigen presentation, gut mucosal immunity, IgA biology and immune dysregulation of the alternative complement system in IgAN [44] and hence exposing possible targets for new interventions. As is common among GWAS though, these identified loci typically have small effect sizes, explaining only 6–8% of the overall disease risk [2]. In contrast, whole exome sequencing (WES) can locate rare gene variants (minor allele frequencies <1% in the population), home in on the excess burden of rare SNVs on specific genes and provide direct causal inferences on disease

pathogenesis. Between these techniques, a genome-wide polygenic risk score could be compiled for an individual suspected of having IgAN, identifying those with higher scores and at greater risk of disease manifestation and likelihood of renal injury leading to ESKD. It would help stratify patients into risk categories, and those at the highest percentiles would warrant early interventions to preempt disease progression and avert the need for dialysis/transplantation in the first place. Similarly, these individuals could be monitored more closely for recurrence post-transplant. Employment of innovations such as exome chips could increase efficiencies and lower cost of screening for rare coding variants in complex diseases, an invaluable tool in the search for the genetic basis of a condition such as IgAN.

Genetic testing's Achilles' heel though remains that many of these gene variants/panels were discovered in a reference population consisting mainly of European descent, and validation in other populations remains sketchy. Furthermore, genetic risk scores only capture part of the evolution of a convoluted disease such as IgAN, and the complex interplay with environmental factors could either diminish or accentuate any genetic underpinnings. Nonetheless, it is a positive first step towards a "precision" approach in the diagnosis and search for the elusive "heritability" of glomerulonephritis such as IgAN.

5. Diagnosis

Non-invasive laboratory tests are currently not available to diagnose recurrent IgAN. Diagnosis of recurrent IgAN is ultimately carried out by biopsy of the kidney transplant. Recurrence of IgAN after kidney transplantation can be suspected in patients with known history of IgAN who have worsening proteinuria, hematuria, and/or rising in serum creatinine [45]. However, IgAN recurrences are commonly seen without clinical signs and can be seen in up to 18% of biopsies with histologic recurrence of IgA deposition [6]. Histological features of IgAN include mesangial hypercellularity on light microscopy, dominant or co-dominant mesangial deposits of IgA on immunofluorescence microscopy, and electron-dense deposits primarily in the mesangium on electron microscopy [10,46]. Oxford classification for IgAN developed by the international IgAN network in collaboration with Renal Pathology Society can be used since it is shown to have prognostic values for kidney transplants [47,48].

6. Treatment

The fundamentals in treating recurrent IgAN center on traditional strategies for nephrotic syndrome; optimized blood pressure control and proteinuria reduction. The use of an ACEi or angiotensin receptor blockers (ARB), which can help lower intraglomerular and systemic pressures in conjunction with its antiproteinuric effects, can possibly delay progression of renal disease [49,50]. High-dose fish oils are also reported to have possible benefits [51]. Tonsillectomy has some evidence of benefit, but studies are mostly limited to the Asian population [52,53]. Other methods of treatments are inferred from studies of IgAN in the native kidneys.

Beyond targeting the RAAS, mineralocorticoid receptor antagonists (MRA) such as finerenone and eplerenone are being used to further help reduce proteinuria in patients with CKD [54,55]. MRA has also been shown to slow the progression of renal disease and cardiovascular events which can apply to patients with IgAN, but direct evidence of its efficacy in recurrent IgAN post-transplant remains lacking [30,56].

Sodium-glucose cotransporter-2 (SGLT2) inhibitors, which were originally developed for treating DM but quickly found to have salubrious effects on cardio-renal outcomes, are being used in patients with CKD and proteinuria in the absence of DM to slow disease progression and reduce cardiovascular events [57,58]. Possible adverse events such as urinary tract infections and amputations have been a concern for SGLT2 inhibitor use in the immunosuppressed population, but emerging evidence shows no higher complication rates compared to its use in post-transplant DM [59]. A pre-specified analysis of the DAPA-CKD trial looked at the use of dapagliflozin specifically in native IgAN patients, randomizing

patients to dapagliflozin 10 mg qday vs. placebo in addition to standard of care [60]. At a median follow-up of 2.1 years, 4% of those on dapagliflozin vs. 15% on placebo (HR 0.29; 95% CI, 0.12–0.73) reached primary endpoint (sustained eGFR decline ≥50%, ESKD, death from kidney-related or cardiovascular causes). Degree of albuminuria was lowered by 26% relative to controls. Serious adverse events were no different between groups. Overall, dapagliflozin demonstrated reduced CKD progression with acceptable safety profile.

Dual endothelin angiotensin receptor antagonists (sparsentan) have been recently approved by the FDA for patients with IgAN at risk for rapid disease progression. Endothelin-1 is strongly associated with podocyte damage and the dual blockade of endothelin-1 and angiotensin II pathways can lead to reduction in proteinuria and help prevent further glomerulosclerosis [61,62]. Early results have suggested a meaningful decrease in proteinuria compared to conventional ARB therapy in patients with IgAN [8].

In terms of immunosuppressive therapy, corticosteroid pulsing has shown significant reduction in renal function decline and progression to ESKD in non-transplant patients with IgAN. One study showed a significantly lower incidence of doubling in serum creatinine at 2% versus 30% during 10 years of follow up [63], while another study showed significantly lower incidence of ESKD at 2% versus 14% at 8 years [64]. However, the efficacy and safety of additional corticosteroid dosing in a transplant population who may already be on maintenance steroids for their allograft is unclear. The addition of calcineurin inhibitors (CNI) in recurrent IgAN will not be further discussed given that >90% transplant patients at most transplant centers are already on a CNI-based immunosuppressive regimen.

Corticosteroid withdrawal regimens gained popularity in the mid-2000s as clinicians lauded the avoidance of the long-term side effects of steroid use without jeopardizing allograft outcomes [65]. Yet, those at risk of recurrent glomerulonephritis post-transplant may not fare as well on a steroid minimization pathway as shown in multiple studies. Data from the Australia and New Zealand Dialysis and Transplant Registry looking at first kidney transplant recipients between 1988–2007 whose original ESKD was from IgAN, found that 12.6% of allograft were lost to recurrent disease. At 5 years, 64% of patients were still on steroid maintenance. On multivariate analysis accounting for recipient's age, sex, HLA mismatch, dialysis vintage and transplant era, corticosteroid use was associated with a lower risk of recurrent IgAN (subhazard ratio [sHR] of 0.5, 95% CI 0.3–0.84) [16]. Further reaffirming evidence came from a study in Turin, Italy, where investigators followed 120 IgA patients who underwent kidney transplants at a single center between 1995 and 2012. Of these, 51 patients underwent an indication biopsy yielding an IgAN recurrence rate of 55% (28/51). Recurrent IgAN was shown to be strongly associated with steroid withdrawal at the time of the biopsy (OR 7.7, $p = 0.03$), while the use of other maintenance immunosuppression or induction agents showed no effects on recurrent disease except for cyclosporine A (32% in recurrent IgAN vs. 9%, $p = 0.02$). However, the authors postulated that only a minority of patients ($n = 10$) were on cyclosporine A and they tended to have the longest follow-up, which might have led to lead-time bias [66]. Lastly, here in the USA, a retrospective study looking at the United Network of Organ Sharing/Organ Procurement and Transplantation Network database found that early steroid withdrawal in 2800 versus 9700 transplant recipients on corticosteroid maintenance, IgAN recurrence was lower among those on steroids (sHR 0.66, $p = 0.014$). However, overall patient survival and death censored graft survival showed no differences [67].

In terms of antimetabolite use (namely azathioprine through inhibition of purine synthesis, and mycophenolic acid derivatives through inhibition of T and B lymphocyte proliferation) in the treatment IgAN, much of it is restricted to native disease. Stangou et al. randomized 22 biopsy- proven IgAN patients (eGFR $\geq$ 30 mL/min/1.73 m^2, proteinuria $\geq$ 1 gm/d and well controlled BP on RAAS inhibition and polyunsaturated fatty acids for 6 months) to either methylprednisolone (MP) alone or in combination with azathioprine (MP+AZA) [68]. At 12 months, renal function essentially remained stable, while proteinuria was reduced significantly in both groups. Four patients who had partial remission with MP alone at study's end were able to achieve full response after conversion

to AZA therapy, and half of patients in each group relapsed after therapy was terminated. In addition, Pozzi et al. randomized 207 native IgAN patients to either Group 1 (pulse MP for 3 days on months 1, 3 and 5 and maintained on oral prednisone 0.5 mg/kg every other day plus AZA 1.5 mg/kg daily) or Group 2 (steroids alone) for 6 months. At 4.9 years of follow-up, they found 12.9% of those in Group 1 and 11.3% of those in Group 2 ($p = 0.83$) reached the primary endpoint (50% increase in serum creatinine above baseline) [69]. Proteinuria was significantly reduced from baseline in both groups (2.0 to 1.07 g/day, $p = 0.001$). There was, however, a greater proportion of patients in Group 1 who discontinued treatment prematurely vs. Group 2 (14.9% vs. 2.8%, $p = 0.002$) due to major side effects (Group 1, 16.8% vs. Group 2, 5.7%, $p = 0.01$) including hepatotoxicity, leukopenia and anemia, all of which are known to be related to AZA.

Turning our attention to mycophenolic acid (MPA) derivatives, most of the evidence of its efficacy in IgAN is limited to native kidneys rather than recurrent disease. A meta-analysis looking at eight randomized clinical trials involving 510 patients found no overall differences in rates of disease remission or development of ESKD among regimens that did or did not include mycophenolate mofetil (MMF) [70]. On a sub-analysis, MMF improved renal remission (complete or partial) compared to placebo (three trials, relative risk 2.15; $p = 0.010$) but compared to those on an immunosuppressive regimen without MMF there were no differences (four trials, relative risk 1.14, $p = 0.146$). As for the outcome of ESKD, MMF was not different compared to placebo and those on immunosuppressives without MMF. Risk of adverse events were similar between groups (relative risk 1.10, $p = 0.79$). In a more recent study [71], 170 IgAN adults who received optimized supportive care (BP control with ARB, anemia management, restricted salt intake, avoidance of nephrotoxic drugs) over a 3-month period were then randomized to either MMF 1.5 g/day for 12 months and then 0.75–1.0 g/day for at least 6 months after, or supportive care (SC) alone (open-label, blinded assessment). A total of 7% of those in the MMF vs. 21% in SC group reached the endpoint (composite of doubling serum creatinine, ESKD, or death due to kidney or cardiovascular causes), with an adjusted hazard ratio (aHR) of 0.23; 95% CI, 0.9–0.63. Progression to CKD occurred in 8% of MMF and 27% of SC participants (aHR, 0.23; 95% CI, 0.10–0.57). Of those followed post-trial, 66 in the MMF group discontinued treatment and demonstrated an accelerated decline in eGFR (-2.9 vs. -6.1 mL/min/1.73 m^2) with no observed differences in the adverse events between the two groups. Taken together, compared to placebo or standard of care, MMF appears to have slowed IgAN progression. Due to the paucity of data in recurrent disease post-transplant, one can only surmise that MMF's effect is likely muted given that despite ~90% of kidney transplant recipients being on an immunosuppressive regimen containing MMF (https://srtr.transplant.hrsa.gov/annual_reports/2021/Kidney.aspx#fig:KItx-ped-imsxn-ind, accessed on 12 June 2023), recurrence risks have remained steadfast throughout the years.

Cyclophosphamide use has not consistently shown positive outcomes in treating IgAN. A single center study did show that cyclophosphamide use with prednisone showed a higher rate of renal survival (72% in treatment group versus 6% in those getting only supportive care at 5 years) [72]. However, the Supportive Versus Immunosuppressive Therapy of Progressive IgA Nephropathy (STOP IgAN) trial did not confirm the potential benefit of cyclophosphamide [73], and in fact called into question the safety of such an approach because of higher rates of severe infections and impaired glucose tolerance in the treatment group. Use of cyclophosphamide is generally used as a last resort and can be considered for resistant cases of IgAN that rapidly progress despite being on maximized treatments [74].

Targeted-release formulations of budesonide (TFR-budesonide) are designed to release the drug in the distal ileum (Peyer's patches, a component of the GALT) where it is theorized to be the place where Gd-IgA1 is formed [75]. A large ($n = 150$) randomized, double-blinded study involving patients with IgAN at risk of progressing to ESKD (eGFR of at least 45 cc/min/1.73 m^2, persistent proteinuria ≥ 0.75 g/day, on maximized RAAS blockade), assigned patients in a 1:1:1 ratio to TFR-budesonide 16 mg/day, 8 mg/day or

placebo over a 9-month period [7]. They found those randomized to TFR-budesonide had stabilization of renal function, and a mean reduction in urinary protein-to-creatinine ratio (UPCR) of 24% (compared to an increase of 2.7% in the placebo group). The treatment effect was maintained at 3-month follow up. However, around 25% of those on treatment arm discontinued their assigned therapy, largely due to corticosteroid-induced adverse events. A retrospective study looking at the efficacy of budesonide compared with patients on systemic corticosteroid showed significant reduction in proteinuria of 45% versus 11% in the systemic corticosteroid group [76]. A case report describes the successful treatment of recurrent IgAN with the use of TFR-budesonide [77].

Adrenocorticotropic hormone (ACTH) gel is approved for proteinuria associated with nephrotic syndrome. One small study following 19 patients with IgAN showed a statistically significant improvement in proteinuria for those who were on ACTH (24-h urine of 2.6 g vs. 1.3 g) at 12 months of observation [78]. Again, direct evidence of its efficacy in recurrent IgAN remains elusive.

The use of B cell targeted therapy such as rituximab is ubiquitous in transplantation. It is thus unsurprising that this has been utilized in IgAN to ameliorate disease progression. Specifically looking at a kidney transplant population, Chancharoenthana et al. randomized 64 transplant recipients with biopsy proven recurrent IgAN to either conventional therapy (n = 43) or rituximab (n = 21), all treated with RAAS blockade at baseline [79]. A total of 38% of the rituximab group vs. none of those in controls achieved complete remission, with a greater proportion of those with reduced proteinuria at 12 months. On biopsy, rituximab-treated patients showed less severe endocapillary hypercellularity despite strong IgA deposition compared to conventional treatment. Corroborating these results, Lundberg et al. treated four patients with native kidney IgAN or those with IgA vasculitis with nephritis, with either rituximab or ofatumumab (a humanized anti-CD20 monoclonal antibody) which demonstrated lowered albuminuria and improved renal function with biopsy showing disappearance of subendothelial but not mesangial deposits. Even in the extreme case of crescentic IgAN, re-biopsy at 9 months showed no necrotic lesions [80]. In another open-label, multicenter trial, CKD patients with native IgAN with well controlled blood pressures on ACEi and proteinuria 1g/day at baseline were randomized to either rituximab or placebo. Despite rituximab leading to depletion of B cells and its effects being sustained for 12 months, serum levels of Gd-IgA1, anti-Gd-IgA1 antibodies, proteinuria reduction, renal function did not differ between groups [81]. Rituximab's lack of efficacy in IgAN was hypothesized to be due to the prominent role of mucosal, and particularly intestinal, lymphoid tissue in the pathogenesis of IgAN that may have shielded this compartment from B-cell depleting therapies [82].

Anti-CD20 agents detailed above are ineffective in terminally differentiated plasmablasts and plasma cells, which could be involved in the pathogenesis of IgAN as detailed earlier. A single study by Hartano et al. utilized the proteosome inhibitor, bortezomib, to target native IgAN patients with significant proteinuria (>1 gm/day) [83]. Eight consecutive patients were given four doses of bortezomib at 1.3 mg/m^2 over a 2-week period, and the follow-up was for 1 year. Three patients achieved the study endpoint of complete remission (CR, defined as proteinuria <300 mg/d, median baseline proteinuria was 2.46 g/d), one was lost to follow-up after a month, four had either no or only partial response but then eventually developed ESKD. Those who achieved CR did so at a median of 6 months. Despite the off-label application and investigations of proteosome inhibitors in antibody mediated rejection following kidney transplantation, there are no studies of its use in recurrent IgAN.

As previously explored in the pathogenesis section, Syk is an immunoreceptor associated protein tyrosine kinase. It is found on multiple cell types including B lymphocytes and myeloid cells, whose role in cell signaling for classic immunoreceptors such as B cell receptors and activatory Fc receptors is well characterized. There is growing interest in Syk blockade as a therapeutic target in autoimmunity and inflammatory conditions [39]. On renal biopsy specimens, staining for splice (total- and T-Syk) along with its phosphorylated

(P-Syk) variants found that expression of T-Syk correlated with IgAN severity (as scored by endocapillary and mesangial proliferation according to the MEST-C grading system) [84], while the number of P-Syk cells was directly correlated with proteinuria but inversely proportional to renal function among native IgAN patients [85]. A number of small molecule anti-Syk inhibitors are under development, including R406 (fostamatinib, and its prodrug R788), that binds onto the catalytic domain of Syk has demonstrated efficacy in animal models of immune-mediated thrombocytopenia [86] and systemic lupus erythematosus [87]. Its role in native IgAN was the focus of a proof-of-principle, international clinical trial (NCT02112838). Subjects had optimized blood pressure control with either ACEi or ARB with a 90-day run-in period, were then randomized to either fostamatinib 100 mg, 150 mg twice daily, or placebo. Primary outcome (UPCR at 24 weeks compared to baseline) was not significantly different across groups. In a pre-specified group with baseline UPCR $\geq$ 1 g/g, a dose dependent reduction in proteinuria was seen, albeit not statistically significant. Renal function as measured by eGFR did not change throughout, and eight serious adverse events occurred in six participants in the fostamatinib group (including pancreatitis, transaminitis, septic shock and hematoma out of a total 51 randomized patients) [88]. Its utility in IgAN remains inconclusive at best, pending further studies. Given the novel nature of this therapeutic option, no studies in post-transplant patients with recurrent IgAN have been reported to date.

The role of the complement system (part of the innate immune system) in the pathogenesis of IgAN has been identified as a potential major driver for renal injury in IgAN [89]. The various targets within this complex network of mediators are ripe for development of new therapeutics. Firstly, within the alternative pathway, mesangial C3 deposition with reduced circulating C3 levels has been associated with disease progression and worsened renal function in cases of IgAN [90,91]. A phase II trial of Iptacopan (LNP023), an oral, selective, reversible inhibitor of complement factor B is underway, and interim results at 90 days of treatment demonstrated a 23% reduction in UPCR versus placebo (p = 0.038) [27,92]. Renal function appears preserved in the treatment group, contrasted with an eGFR of -3.3 cc/min/1.73 m^2 in the placebo group. Adverse events were no different between the two groups.

Secondly, mesangial deposition of mannan-binding lectin (MBL), L-ficolin MBL-associated serine protease (MASP) and C4d implicates the lectin pathway in the pathogenesis of IgAN [93]. They are predictive of more severe histologic changes (greater mesangial expansion, extra-capillary proliferation and glomerular sclerosis and interstitial infiltration). A phase II study was completed looking at narsoplimab (OMS721), a humanized monoclonal antibody against MASP-2, to evaluate its safety, tolerability and efficacy in IgAN. In substudy 1, a single arm group receiving 12 weekly infusions of narsoplimab with an additional 6 weeks of follow up showed reduction in 24-h urine protein excretion of 54–95% [94]. Subjects were randomized in 1:1 ratio in sub-study 2 to either receiving a course of weekly infusion of narsoplimab versus placebo, with eight subjects opting to continue into an open-label extension course of narsoplimab infusions at investigator discretion. Mean reduction in 24-h urine protein excretion in the extension group was 64% between weeks 31–54 post-baseline. All patients maintained stable eGFR. Adverse events were mild to moderate, and transient in nature. An ongoing phase III study of patients with albuminuria > 1g/day is underway.

Lastly, any complement activation terminates in the eventual cleavage of C5 into C5a and C5b by C5 convertase, leading to the formation of the C5-9 (membrane attack complex, MAC). The interaction of C5a and C5aR propagates an inflammatory milieu, and emergence of C5a in urine and presence of C5a and C5aR in renal tissue have been correlated with severity of renal injury in IgAN [95]. Eculizumab, a recombinant humanized anti-C5 monoclonal antibody blocks formation of the MAC, was reported as salvage therapy in two case reports after standard therapies have failed, demonstrating initial stabilization of renal function and lowering albuminuria in progressive IgAN. Both patients, however, eventually developed ESKD with established chronicity on biopsy [96,97]. Another option

is avacopan (CCX168), an oral small molecule that selectively antagonizes C5aR, which was studied in an open-label pilot study in IgAN patient with UPCR > 1 g/g and preserved renal function. Seven of the screened patients received avacopan, and six of them had numerical improvements in UPCR, of whom three had reduction in UPCR ~50% at week 12. The improvement in UPCR persisted in five of the patients through week 24. The urinary monocyte chemoattractant 1-to-creatinine ratio was reduced ~30% at week 8, reflecting the anti-inflammatory effects of avacopan. The drug was well-tolerated and one patient had a serious adverse event, unstable angina that was ruled unrelated to avacopan [98].

Another therapeutic area of interest involves the modulation of B cells. Anti-proliferation-inducing ligand (APRIL) and B-cell activation factor (BAFF) are involved in B cell activation and implicated in IgAN pathogenesis. Mouse models of IgAN have demonstrated reduced production of nephritogenic IgA in those receiving an APRIL antagonist. VIS649 is a fully humanized monoclonal IgG2 antibody against APRIL and was studied in a phase I study in healthy volunteers in ascending doses of 0.5 to 12 mg/kg [99]. Of the 47 subjects who received a single intravenous administration of VIS649 and completed the follow up, none had a serious adverse event. Serum IgA, Gd-IgA1, IgG and IgM levels were suppressed in a dose-dependent manner and had a time-to-recovery that too was dose-dependent with reappearance of circulating APRIL in the serum. It provides encouraging signals for potential therapeutic development of the agent in IgAN. Another promising monoclonal antibody, BION-1301, was studied in a phase I/II trial and showed that at a dose of 450 mg given every 2 weeks for a total of 12 weeks in IgAN patients with UPCR $\geq$ 0.5 g/g and on optimized on RAAS inhibition, there were no serious adverse events and that durable reduction in serum levels of free APRIL, and immunoglobulins (IgA, Gd-IgA1, IgM and to a lesser extent IgG) was achievable with the drug. Clinically meaningful reduction in proteinuria with corresponding reduction in IgA levels were observed [100].

With regards to BAFF, this has been linked to B-cell mediated autoimmune conditions, and higher serum levels have correlated with more advanced histologic changes in IgAN (mesangial hypercellularity and segmental glomerulosclerosis) and a potential therapeutic target [101]. Blisibimod, an anti-BAFF monoclonal antibody, was approved as a first-in-class agent for the treatment of systemic lupus erythematosus, demonstrating its efficacy and safety for clinical use. A phase II/III study, BRIGHT-SC was conducted in IgAN patients receiving either subcutaneous injections of study drug or a placebo, who were optimized on RAAS blockade. Results were shared at an American Society of Nephrology meeting as an abstract [102]. The study suggested that suppression of B-cell subset and immunoglobulin levels were seen in the blisibimod group, with a reduction in proteinuria in treatment arm versus a steady increase in placebo (% change from baseline −8.7 vs. +59.4, $p = 0.017$), with no differences in eGFR, with 1 patient from each group progressing to ESKD during the study. Atacicept is a bLys (B-cell stimulator, analogous to BAFF) receptor–antibody fusion protein that targets both BAFF and APRIL, was examined in a phase II study for safety and efficacy at reducing Gd-IgA1 levels and its impact on renal function in IgAN [103]. Interim results at 24 weeks showed those receiving subcutaneous injections of atacicept had a reduction in immunoglobulin (IgA, M and G) and particularly Gd-IgA1 levels, with a parallel % reduction in proteinuria up to −25% in the treatment versus +0.098% in placebo groups. Estimated GFR remained stable throughout. No serious adverse events were reported during the 24 weeks of follow up.

Table 2 summarizes the treatment options for IgAN, both for native and recurrent disease.

Table 2. Treatment Options for Recurrent and Native IgAN.

Drug/Treatment	Study Type	IgAN Type	Synthetic Evidence	References
ACEi	Prospective Cohort Study	Recurrent	ACEis may reduce blood pressure and proteinuria in IgAN post-transplant	Oka et al. [45]
ACEi/ARB	Retrospective Cohort Study	Recurrent	ACEi/ARBs may improve 10-year graft survival in transplanted patients with ESRD due to IgAN	Courtney et al. [46]
Fish Oil	Randomized Controlled Trial	Native	Fish oil may slow renal decline in IgAN	Donadio et al. [47]
Tonsillectomy	Prospective Cohort Study	Recurrent	Tonsillectomy may reduce proteinuria in post-transplant IgAN	Kennoki et al. [49]
Tonsillectomy	Prospective Cohort Study	Native	Tonsillectomy and high-dose steroids may improve clinical remission in those with high-proteinuria IgAN	Miyazaki et al. [48]
SGLT2 Inhibitors	Randomized Controlled Trial Sub-analysis	Native	Dapagliflozin may reduce the risk of CKD progression in those with IgAN	Wheeler et al. [56]
Dual Endothelin-Angiotensin Receptor Antagonist	Randomized Controlled Trial	Native	In IgAN, sparsentan may reduce proteinuria compared to irbesartan	Heerspink et al. [8]
Corticosteroids	Randomized Controlled Trials	Native	In patients with IgAN and proteinuria, steroids (including monthly pulse methylprednisolone) may protect against worsening renal function	Pozzi et al. [69], Manno et al. [59]
Steroid Withdrawal	Retrospective Cohort Studies	Recurrent	Early steroid withdrawal post-transplant may increase risk for recurrent IgAN	Di Vico et al. [62], Leeaphorn et al. [63], Clayton et al. [17]
Cyclophosphamide	Randomized Controlled Trial	Native	For high-risk IgAN, adding immunosuppressive agents including cyclophosphamide may not improve outcomes and increases adverse events	Rauen et al. [69]
TRF-budesonide	Randomized Controlled Trial	Native	TRF-budesonide may stabilize renal function and reduce proteinuria in IgAN, but also may increase adverse events	Fellstrom et al. [7]
TRF-budesonide	Case Report	Recurrent	TRF-budesonide may lead to clinical remission in post-transplant IgAN	Lingaraj et al. [73]
ACTH	Prospective Cohort Study	Native	ACTH gel may reduce proteinuria and stabilize renal function in IgAN	Zand et al. [74]
Iptacopan (complement Inhibitor)	Randomized Controlled Trial (Phase II)	Native	Iptacopan may reduce proteinuria and preserve renal function	Perkovic et al. [23]
Narsoplimab (anti-MASP-2 monoclonal Ab)	Prospective Cohort Study	Native	Narsoplimab may reduce proteinuria and stabilize renal function in advanced IgAN	Lafayette et al. [90]
Eculizumab (anti-C5 monoclonal Ab)	Case Reports	Native	Eculizumab may reduce proteinuria and stabilize renal function in progressive IgAN	Ring et al. [92], Rosenblad et al. [93]

Table 2. *Cont.*

Drug/Treatment	Study Type	IgAN Type	Synthetic Evidence	References
Avacopan (anti-C5aR small molecule)	Prospective Cohort Study	Native	Avacopan may reduce proteinuria in IgAN	Bruchfeld et al. [94]
BION-1301 (anti-APRIL monoclonal Ab)	Phase I/II Clinical Trial	Native	BION-1301 may reduce IgA and Gd-IgA1 levels and proteinuria in IgAN	Barratt et al. [96]
Blisibimod (anti-BAFF monoclonal Ab)	Randomized Controlled Trial (Phase II)	Native	Blisibimod may reduce proteinuria in IgAN	Barratt et al. [102]
Atacicept (anti-bLyS fusion protein)	Randomized Controlled Trial (Phase II)	Native	Atacicept may reduce Gd-IgA1 levels and proteinuria in IgAN	Barratt et al. [98]
Bortezomib	Prospective Cohort Study	Native	Bortezomib may reduce proteinuria in some cases of IgAN	Hartono et al. [79]
Fostamatinib (SYK inhibitor)	Randomized Controlled Trial (Phase II)	Native	Fostamatinib may reduce proteinuria in IgAN	Tam et al. [84]
Rituximab	Randomized Controlled Trial	Native	Rituximab may not significantly reduce proteinuria in IgAN	Lafayette et al. [77]
Mycophenolate	Randomized Controlled Trial	Native	In progressive IgAN, mycophenolate may reduce kidney disease progression	Hou et al. [67]
Azathioprine	Randomized Controlled Trial	Native	In IgAN, adding azathioprine to steroids may not reduce risk of kidney disease progression	Pozzi et al. [65]

Abbreviations: IgAN—IgA nephropathy; ACEi—angiotensin converting enzyme inhibitor; ARB—angiotensin receptor blocker; SGLT2 -sodium-glucose cotransporter-2; CKD—chronic kidney disease; TRF—targeted release formulation; ACTH—adrenocorticotropic hormone; MASP-2—mannose-binding lectin associated serine protease 2; Ab—antibody; C5aR—C5a (complement) receptor; Gd-IgA1—galactose-deficient IgA1; APRIL—A proliferation-inducing ligand; BAFF—B cell activating factor; bLyS—B lymphocyte stimulator; SYK—spleen tyrosine kinase; RAAS—renin-angiotensin-aldosterone system.

7. Prognosis

In those with recurrent IgAN, investigators have looked at prognostic factors that portend worse allograft outcomes. Among 80 recurrent patients, Kavanagh et al. identified that serum creatinine at biopsy, longer duration since transplant, higher levels of proteinuria, the combined MEST-C score (part of the Oxford classification for IgAN), and concurrent rejection were all associated with higher rates of allograft failure [104]. On Cox multivariate analysis, only the MEST-C score no longer held up statistically significant as a predictor of worse outcomes, while higher degrees of HLA matching between donor–recipients had a positive impact on allograft survival. Large registry analysis demonstrate that IgAN recurrence is a significant cause of graft loss, however, overall long-term outcomes of patients with IgAN are similar to that of patients with other types of glomerulonephritis and other causes of ESKD [4,16,20]. Large case series have demonstrated that IgAN recurrence does have an impact on long term graft survival [45,105].

8. Future Directions

The burden of recurrent glomerulonephritis continues to weigh on the long-term survival of kidney allografts, especially as rates of rejection and infectious complications have dramatically fallen with the improvement in immunosuppressive and antimicrobial regimens that have traditionally limited short-term outcomes. There remain large knowledge gaps in the risk stratification of those at greatest risk of recurrent IgAN, but the advent of genomics will hopefully herald a "personalized" approach to the care of this

population. Work needs to be carried out on identifying noninvasive biomarkers for the early detection of recurrent disease as opposed to relying on insensitive urinary parameters or rising serum creatinine that occur late in the setting of established, irreversible injury. New lines of therapies are on the horizon, which may lead to more effective treatment that targets specific mechanisms by which recurrent IgAN occurs, stemming the allograft injury right at its source. New discoveries are driven by GWAS studies that seek to unearth novel pathways through which IgAN impacts kidney allograft function. Only through these concerted efforts can appalling rates of late allograft losses be addressed, especially as the number of patients on the organ waitlist continues to grow exponentially.

9. Conclusions

IgAN remains a significant contributor to the worldwide burden of ESKD and represents a significant proportion of patients who undergo kidney transplantation. Its recurrence in an allograft is under-recognized due to the inconsistent practice of protocol biopsies across transplant centers. As such, recurrent IgAN may well be a formidable cause of late-onset allograft failure, and thus a threat to long term kidney allograft survival. There are currently no definitive, non-invasive methods at diagnosing this condition, and often by the time clinicians are aware of the negative impact that recurrent IgAN disease has on kidney function, the injury is already well established and likely irreversible. Even when picked up early, there are currently limited therapeutic options, mostly limited to non-specific measures to lower proteinuria rather than directed treatment. Recent developments in the understanding of underlying genetic susceptibility, mechanisms of renal injury, and novel guided therapeutics that are on the horizon have invigorated interest and research in this orphan condition. The ability to adopt a more "personalized" strategy to managing post-transplant recurrent IgAN may be just right around the corner.

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