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Recurrence of immunoglobulin A nephropathy after kidney transplantation: a therapeutic gap in the era of targeted therapies

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Immunoglobulin A nephropathy (IgAN) frequently recurs after kidney transplantation and remains an underrecognized cause of allograft loss. Although targeted-release budesonide, B-cell modulators, and complement inhibitors have transformed native IgAN treatment, transplant recipients were excluded from trials, leaving management based largely on case reports, small series, and registry data. Reported recurrence rates range from 10% to 30% at 10–15 years after transplant, depending on biopsy practices and diagnostic criteria. Younger age, preemptive transplantation, and rapid progression to end-stage kidney disease are the most consistent risk factors. Two large registries suggested that maintenance corticosteroids reduce recurrence, but this association was not confirmed in propensity-matched or multicenter studies, and induction immunosuppression was not adequately accounted for. Recurrence significantly worsens graft survival, with hazard ratios for graft loss ranging from 2 to nearly 4. Mechanistically, IgAN is increasingly viewed as a disorder of B-cell and plasma-cell biology driven by the B-cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL) axis, which may explain why T-cell-focused immunosuppression to prevent rejection fails to prevent recurrence. Early experience with B-cell-, plasma-cell-, and complement-targeted therapies after transplantation is encouraging but limited. Progress will require harmonized registries, validated biomarkers, industry collaboration, and dedicated randomized trials in transplant recipients.

KEYWORDS
allograft survival, B cells, BAFF/APRIL, complement inhibition, disease recurrence, IgAN, kidney transplantation

The evolving landscape of immunoglobulin A nephropathy: from native disease to post-transplant recurrence

The previous decade has seen substantial advancement in the treatment of immunoglobulin A nephropathy (IgAN), with more targeted therapies developed than for any other primary glomerulonephritis (GN). The recognition of IgAN as a more aggressive condition than previously believed, even in patients with only moderate proteinuria [1, 2], combined with the acceptance of proteinuria as a surrogate endpoint

for clinical trials [3], has attracted investment and driven innovation in a field where only repurposed therapies from other diseases had previously been explored. In 2021, the United States Food and Drug Administration (FDA) granted accelerated approval for targeted-release budesonide for the treatment of IgAN, the first medication approved for this disease [4]. Since then, the FDA has not only granted full approval to this molecule, but has also granted accelerated or full approval to at least five additional molecules for the treatment of IgAN as of this writing. In 2025, the Kidney Disease: Improving Global Outcomes (KDIGO) updated its guidelines on IgAN, only to release a commentary 6 months later updating the treatment algorithm to include B-cell modulators [5, 6], a testament to the rapidly evolving landscape of IgAN.

The advancements in the treatment of recurrent IgAN following kidney transplantation do not parallel those seen in native disease. This is due, in part, to the exclusion of kidney transplant recipients from clinical trials on IgAN [7]. As long-term allograft survival improves, recurrent IgAN is becoming an increasingly important contributor to late graft dysfunction, yet management remains guided by isolated case reports, small case series, and expert opinion. Herein, we review the epidemiology, pathogenesis, and clinical impact of recurrent IgAN, summarize lessons from available registries, and discuss the emerging role of disease-specific therapies in the transplant setting.

IgAN recurrence: epidemiology, risk factors, and clinical impact

Incidence of IgAN recurrence after kidney transplantation

The incidence of IgAN recurrence after kidney transplantation has been reported at highly variable rates, mainly dependent on region, biopsy indication (for cause vs. protocol), and the definition used for recurrent disease [8, 9]. For instance, Jean Berger, who is credited with the identification of IgAN, described a high incidence of recurrent IgAN in 17 out of 32 patients (53.1%) who received kidney transplantation. Notably, all of these patients underwent serial protocol biopsies performed per institutional practice [10]. Recurrence was defined by the presence of mesangial deposits with positive immunoglobulin A (IgA) staining on immunofluorescence. Modern registries report more conservative recurrence rates, typically averaging 20%–30% at 10–15 years post-transplantation [11, 12]. One such registry examining recurrent IgAN after kidney transplantation collected data from 504 transplant recipients with IgAN across 16 centers in Europe, North America, and South America [12]. This initiative, part of the Post-Transplant Glomerular Diseases (TANGO) consortium, identified a cumulative incidence of recurrence of 23% at 15 years. Notably, only patients with biopsy-proven native diagnosis of IgAN were included, and 95% of those with recurrent IgAN had for-cause rather than protocol biopsies. Data on recurrent post-transplant IgAN from the Australia and New Zealand Dialysis and Transplant registry (ANZDATA), Reported an incidence of recurrence of only 10.8% at 10 years [13]. The incidence of recurrence in this registry is significantly lower than that reported in earlier studies, which may be explained by differences in biopsy ascertainment, diagnostic classification, population homogeneity, and sample size.

Histopathology of recurrent IgAN

Histologic recurrence spans a spectrum from isolated mesangial IgA deposition without light-microscopic changes, frequently detected on protocol biopsies, to mesangioproliferative, endocapillary proliferative, and crescentic GN. Mesangial IgA deposition may be detected in protocol biopsies in otherwise stable recipients and does not invariably predict progressive allograft dysfunction. Conversely, patients presenting with proteinuria and declining graft function frequently have concurrent pathologies, including chronic antibody-mediated rejection, transplant glomerulopathy, calcineurin inhibitor toxicity, or interstitial fibrosis/tubular atrophy. Therefore, interpretation of recurrent IgAN requires integration of histologic findings with clinical presentation. Because IgA deposits alone carry limited prognostic weight, the Oxford MEST-C classification (mesangial [M] and endocapillary [E] hypercellularity, segmental sclerosis [S], interstitial fibrosis/tubular atrophy [T], and crescents [C]), developed and validated in native IgAN, has been increasingly applied to allograft biopsies. In 57 North American recipients with recurrent IgAN, a higher total MEST-C score was associated with death-censored graft failure (adjusted hazard ratio (HR) 8.57 [95% confidence interval (CI) 1.23–59.85] for scores 2–3 and 61.32 [95% CI 4.82–779.89] for scores 4–5 vs. 0), as were E, T, and C individually ($p < 0.05$ each), findings concordant with earlier South Korean cohorts [14, 15].

The role of protocol biopsies in transplant recipients with IgAN remains undefined. Protocol-biopsy series detect histologic recurrence earlier and more frequently than for-cause biopsies, often in recipients with normal urinalysis [16]. However, the natural history of this subclinical recurrence is poorly characterized: available longitudinal data are limited to small series in which some recipients progressed to overt disease while others remained stable or showed clearance of deposits on subsequent biopsy [17]. Whether intervening at this stage improves graft outcomes has not been studied. In the absence of such data, we favor a risk-adapted approach with a low threshold for for-cause biopsy in recipients with new hematuria, proteinuria, or unexplained estimated glomerular filtration rate (eGFR) decline, while acknowledging that systematic protocol biopsies within prospective registries will be needed to define the clinical significance of subclinical recurrence.

Risk factors associated with IgAN recurrence

Common risk factors associated with post-transplant IgAN recurrence include younger age at transplantation, a shorter interval from IgAN diagnosis to kidney failure, preemptive transplantation, and a shorter time on dialysis (Table 1). Together, these factors point to a native disease course that was either aggressive or had not yet reached quiescence at the time of transplantation [9, 11, 12, 18].

Whether maintenance corticosteroids protect against IgAN recurrence after kidney transplantation remains debated, and much of the evidence traces back to a single influential registry

TABLE 1 Risk factors associated with IgAN recurrence after kidney transplantation.

Risk factor	Direction	Comment
Younger age at transplantation	↑ risk	Consistently identified across registries; one of the most robust predictors [9, 11, 12, 18].
Shorter interval from IgAN diagnosis to kidney failure	↑ risk	Suggests a more aggressive native disease course [9, 11, 12, 18]
Preemptive transplantation	↑ risk	Reproducible finding; may reflect transplantation before native disease activity had quiesced [9, 11, 12, 18].
Shorter time on dialysis	↑ risk	Conceptually overlaps with preemptive transplantation; same "insufficient quiescence" rationale [9, 11, 12, 18].
Steroid maintenance vs. withdrawal	Inconsistent evidence	ANZDATA and UNOS/OPTN suggested a protective effect of steroid maintenance, but neither adjusted for induction immunosuppression; more rigorous designs (USRDS propensity-matched, steroid-free cohort, TANGO multivariable) found no significant association [12, 19–21].
Preformed DSA at transplantation	↑ risk	HR 2.74 (TANGO); based on a small number of DSA-positive patients with recurrence — interpret cautiously [12].
De novo DSA after transplantation	↑ risk (larger effect)	HR 6.05 (TANGO), greater than preformed DSA; authors propose inadequate immunosuppression as a shared driver of both DSA formation and recurrence; likewise limited by small numbers [12].

Abbreviations: ANZDATA, australia and new zealand dialysis and transplant registry; DSA, donor-specific antibody; HR, hazard ratio; IgAN, immunoglobulin A nephropathy; OPTN, organ procurement and transplantation network; TANGO, Post-Transplant Glomerular Diseases consortium; UNOS, united network for organ sharing; USRDS, united states renal data system.

analysis. A survival analysis using ANZDATA examined 1,521 first-transplant recipients with IgAN-related kidney failure (1988–2007) and modeled steroid use as a time-varying covariate in a competing-risk framework. After adjusting for age, sex, human leukocyte antigen (HLA) mismatch, dialysis duration, and transplant era, steroid use was associated with a markedly reduced risk of recurrence-related graft loss (subhazard ratio 0.50, 95% CI 0.30–0.84) [19]. This finding was influential enough that steroid maintenance became a common default in IgAN recipients, and it found apparent confirmation in a second large registry study: an analysis of 9690 United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) recipients (2000–2014), similarly reported that early steroid withdrawal carried a higher risk of recurrence-attributable graft loss relative to steroid continuation (subhazard ratio 0.666, 95% CI 0.482–0.921), with no difference in overall patient or death-censored graft survival between groups [20].

Both studies, however, share a structural limitation that bears directly on causal interpretation: neither adjusted for induction immunosuppression as an explicit covariate. This matters because steroid-avoidance and steroid-withdrawal protocols are rarely implemented in isolation. Notably, in the ANZDATA registry only 26% of the patients on this cohort received induction therapy, and none of those who received induction therapy lost the graft to IgAN. If induction agent independently influences recurrence risk, as later data suggest, its imbalance between steroid-continued and steroid-withdrawn groups could confound the apparent steroid effect.

More recent studies designed to address these limitations have not reproduced the protective steroid signal. For instance, a propensity score matched analysis using the United States Renal Data System (USRDS) data found no adverse effect of early steroid withdrawal on graft loss from recurrent GN, including IgAN [22]. Another single-center experience with a steroid-free protocol reported a recurrence rate (13.6%) and graft/patient survival comparable to steroid-based national UNOS benchmarks over a 10-year period [21]. In the multivariable analysis by the international TANGO cohort, early steroid withdrawal was not significantly associated with recurrence [12].

Taken together, the evidence for a protective effect of steroid maintenance is based primarily on two large but methodologically similar registry analyses. Studies employing propensity matching or broader multivariable adjustment, including donor-specific antibodies (DSA) and induction data, have not confirmed this association, instead pointing to preemptive transplantation, and a faster progression to kidney failure as the more consistent drivers of recurrence. Current evidence therefore remains conflicting and insufficient to support steroid maintenance solely for the prevention of recurrent IgAN.

The presence of DSA at the time of transplantation has also been observed to correlate with recurrence risk in several registries, including the TANGO cohort (HR 2.74, 95% CI 1.22–6.14; $p = 0.01$) [12]. Interestingly, development of *de novo* DSA after transplantation was associated with an even greater risk of subsequent IgAN recurrence (HR 6.05, 95% CI 2.91–12.61; $p = 0.001$). The authors propose that this association may reflect inadequate immunosuppression as a shared underlying driver of both *de novo* DSA formation and disease recurrence. These findings should nonetheless be interpreted with caution, given the small number of patients with preformed or *de novo* DSA who experienced recurrence within this cohort.

Other transplant-related variables—including donor type, living related donation, HLA matching, induction strategy, and maintenance immunosuppression—have not been consistently associated with recurrent IgAN. The available evidence is largely

derived from retrospective studies with heterogeneous biopsy practices, precluding firm conclusions regarding the independent contribution of these factors.

Clinical impact of IgAN recurrence in kidney transplants

Recurrence of glomerular disease after kidney transplantation negatively impacts allograft survival regardless of etiology, ranking as the third leading cause of graft loss at 10 years, behind only chronic rejection and death with a functioning graft. The impact of recurrent IgAN on graft survival, however, may be less apparent than the one of other glomerular diseases, for at least two reasons: first, recurrence typically becomes clinically manifest only several years after transplantation, and second, the natural history of IgAN itself tends to be one of slow, indolent progression rather than rapid graft loss [23]. Comparative data from USRDS support a relatively favorable allograft survival profile for IgAN among transplant recipients with GN. In a cohort of over 32,000 patients with GN as the primary cause of end-stage kidney disease (ESKD), IgAN recipients had the lowest rate of all-cause allograft failure among the GN subtypes studied (3.5 events per 100 person-years) [24]. Positioned within the broader spectrum of ESKD etiologies, IgAN's allograft outcomes were second only to autosomal dominant polycystic kidney disease (HR 0.93 for all-cause failure, 0.85 death-censored) and notably more favorable than diabetic nephropathy (HR 1.63 all-cause, 1.16 death-censored), reinforcing that despite its propensity to recur, IgAN as a primary disease confers a comparatively benign allograft trajectory relative to most other GN.

However, when analyses isolate the specific impact of recurrence itself, a different picture emerges. A study on 2,501 IgAN transplant recipients based on an ANZDATA cohort found that recurrence carried a substantial allograft cost: 5-year death-censored graft survival following recurrent IgAN was only 58%, comparable to focal segmental glomerulosclerosis (FSGS) and membranous nephropathy but considerably better than membranoproliferative glomerulonephritis (30%) [25]. Data from the TANGO cohort similarly reinforce the impact of IgAN recurrence on graft survival: 10-year death-censored graft survival was 76% among patients with recurrence versus 89% among those without [12]. Importantly, the authors recognized that this comparison was susceptible to immortal time bias, artificially favoring the recurrence group in a naive analysis. To correct for this, they modeled IgAN recurrence as a time-varying covariate, an approach that more appropriately accounts for the timing of recurrence relative to graft loss. This adjusted analysis yielded a hazard ratio of 3.7 for graft loss among patients with recurrent IgAN compared with those without, underscoring that the true magnitude of recurrence's impact on graft survival may be considerably greater than a simple comparison of survival curves would suggest.

Pathogenesis of IgAN and its implication for post-transplant recurrence

In IgAN, a sequence of pathogenic events culminates in the deposition of immune complexes within the renal mesangium, triggering mesangial cell activation and proliferation, release of pro-inflammatory cytokines, and complement activation, ultimately manifesting as glomerular injury and fibrosis. This cascade is conceptualized as the "four-hit hypothesis," which begins with the overproduction and increased circulation of a pathogenic IgA variant deficient in galactose (Gd-IgA1) within the O-glycans of the hinge region [26–30]. The exposed N-acetylgalactosamine residues on Gd-IgA1 are recognized by anti-glycan autoantibodies, predominantly immunoglobulin G (IgG) and, to a lesser extent, IgA, and this interaction generates circulating immune complexes that deposit in the mesangium, driving renal injury (Figure 1) [31].

Although circulating Gd-IgA1 levels are higher on average in IgAN, substantial overlap with healthy individuals limits the diagnostic and prognostic performance of current assays and suggests that Gd-IgA1 concentration alone is insufficient to explain disease expression [32–36]. Mass spectrometry can provide more detailed, site-specific characterization of IgA1 glycoforms, but its analytical complexity and limited throughput currently constrain large-scale clinical implementation [37]. Some studies also identified Gd-IgA1 directly targeting mesangial antigens, which would not require the formation of immune complexes for disease initiation and progression [38–40].

Central to the first two hits of this cascade are B-cells and plasma cells. Over the past decade, a substantial body of evidence has shifted attention away from the immune complexes themselves and toward the aberrant B-cell biology responsible for generating Gd-IgA1 in the first place, implicating dysregulated cytokine signaling in B-cell maturation, class-switching, and survival [41–43]. Two cytokines of the tumor necrosis factor (TNF) superfamily, B-cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL), have emerged as particularly important regulators of IgA biology and IgAN pathogenesis, positioning them as candidate upstream therapeutic targets. BAFF acts primarily through the BAFF receptor (BAFF-R) and is critical to the maturation of transitional B-cells, while APRIL binds with high affinity to transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI) and B-cell maturation antigen (BCMA), both more highly expressed at later stages of B-cell maturation; APRIL signaling through these receptors drives class-switch recombination and supports the long-term survival of memory B-cells and plasma cells [44].

Both cytokines have been implicated in IgAN pathogenesis through translational studies correlating elevated BAFF and APRIL levels with elevated Gd-IgA1, and through murine models that illustrate their mechanistic roles: BAFF-transgenic mice overexpressing BAFF develop an IgA-dominant GN with abnormally glycosylated circulating IgA, while APRIL-deficient and TACI-deficient mice show reduced IgA levels [42, 45–50].

The growing recognition that Gd-IgA1 production by B-cells and plasma cells is affected by BAFF/APRIL axis, has provided the rationale for BAFF and APRIL targeted therapies in IgAN. Sibeprenlimab, an APRIL inhibitor, received FDA accelerated approval in November 2025 based on proteinuria reduction in phase 3 data [51], and atacicept, a TACI-Ig fusion protein that blocks both BAFF and APRIL, followed with its own FDA accelerated approval in July 2026 [52, 53]. Taken together, this

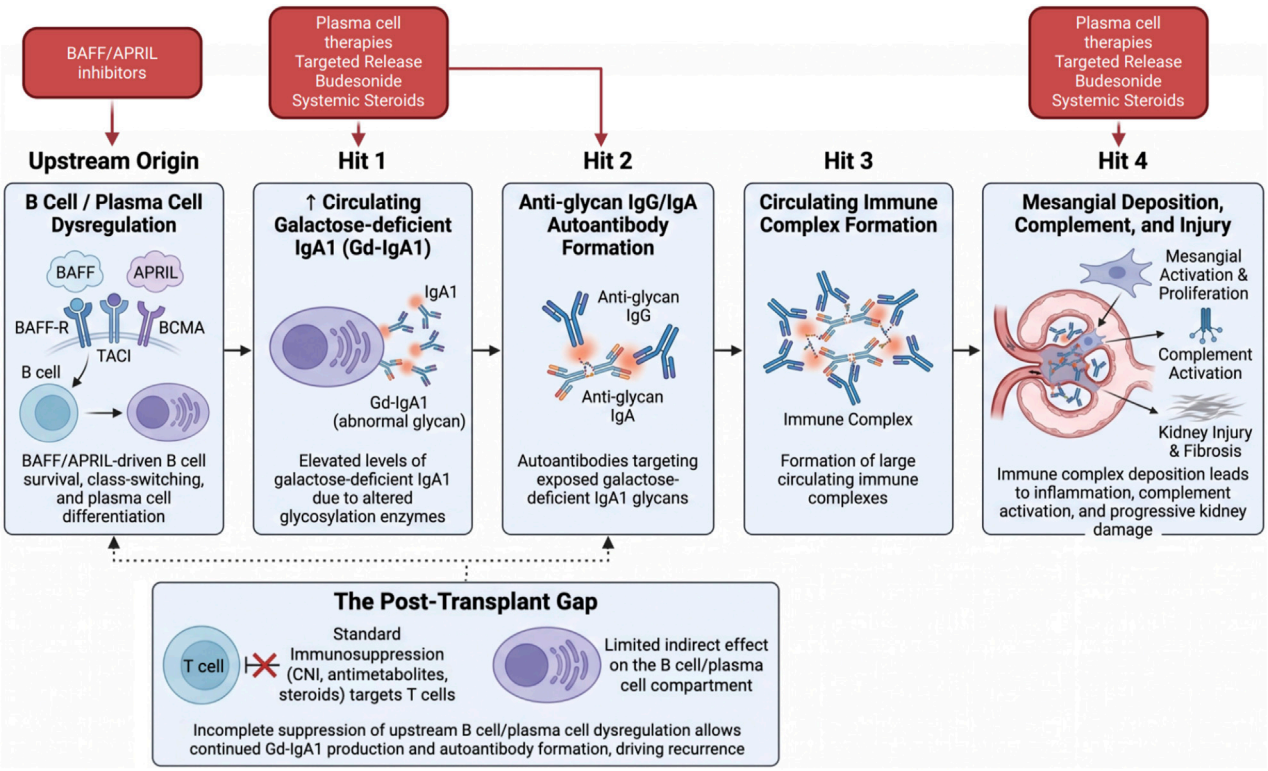


FIGURE 1
The four-hit hypothesis of IgAN pathogenesis and the immunologic gap in post-transplant immunosuppression. B-cell and plasma cell dysregulation via the BAFF/APRIL axis drives a four-hit cascade: Hit 1, increased circulating galactose-deficient IgA1 (Gd-IgA1); Hit 2, anti-glycan IgG/IgA autoantibody formation against Gd-IgA1; Hit 3, circulating immune complex formation; Hit 4, mesangial deposition causing mesangial cell activation, complement activation, and progressive injury/fibrosis. Targeted therapies (BAFF/APRIL inhibitors, plasma cell-directed agents, targeted-release budesonide, systemic steroids) are mapped to the steps they intercept. Standard transplant immunosuppression (calcineurin inhibitors, antimetabolites, corticosteroids) targets T cell–mediated alloimmunity but has limited direct effect on the B cell/plasma cell compartment driving Hits 1–2, allowing persistent Gd-IgA1 and autoantibody production despite adequate immunosuppression, a rationale for B cell- and plasma cell-targeted therapies in preventing post-transplant recurrence. Abbreviations: APRIL, a proliferation-inducing ligand; BAFF, B-cell–activating factor; CNI, calcineurin inhibitor; Gd-IgA1, galactose-deficient IgA1; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IgG, Immunoglobilun G. Figure created in Biorender.com.

evidence reframes IgAN less as a disease of immune complex deposition *per se*, and more fundamentally as one of dysregulated B-cell and plasma cell biology, a framing directly relevant to the question of why disease recurs after transplantation despite immunosuppressive regimens.

The persistence of disease despite successful transplantation highlights a fundamental distinction between alloimmunity and autoimmunity. Conventional immunosuppressive regimens effectively suppress T-cell activation and indirectly inhibit B-cell responses but have relatively limited effects on long-lived plasma cells and mucosal immune compartments responsible for ongoing Gd-IgA1 production. This biological mismatch provides a plausible explanation for why recurrent IgAN develops despite adequate prevention of rejection and further supports targeting upstream B-cell and plasma-cell pathways.

Biomarkers of post-transplant IgAN recurrence largely mirror those implicated in native disease. Elevated levels of Gd-IgA1 and APRIL have both been reported in patients with recurrent IgAN following kidney transplantation; however, their association with recurrence risk has so far been reported only in small cohorts with variable follow-up periods and non-standardized assay measurements [9, 54]. Notably, Gd-IgA1 deposition has been detected in renal allografts biopsied as early as 1 hour post-transplantation [55]. A recent meta-analysis pooling eight studies found that serum Gd-IgA1 levels were significantly higher overall in patients who developed recurrence than in those who did not (standardized mean difference 0.50, 95% CI 0.15–0.85, $p = 0.005$). Pretransplant levels, by contrast, did not differ significantly between groups [56]. Together, these findings suggest Gd-IgA1 may hold more value as a post-transplant marker of active recurrence than as a pretransplant risk-stratification tool.

APRIL has similarly been investigated as a candidate biomarker. In a cohort of 33 patients with biopsy-proven native IgAN undergoing kidney transplantation, pretransplant serum APRIL levels did not differ significantly between patients who would later develop recurrence and those who would not (15.6 ± 15.7 pg/mL vs. 16.8 ± 10.8 pg/mL, p = 0.611); however, mean post-transplant APRIL levels remained persistently elevated in the recurrence group for up to 3 years [57]. As with Gd-IgA1, this suggests that serial post-transplant monitoring, rather than a single pretransplant measurement, may ultimately prove more clinically useful once a validated, commercially available assay is developed.

Future biomarker development will likely extend beyond circulating Gd-IgA1 and APRIL measurements. Integration of donor-derived cell-free DNA, urinary immune biomarkers, complement activation products, tissue immune phenotyping, multiplex imaging, and spatial transcriptomic approaches may allow improved discrimination between active recurrent disease, concomitant alloimmune injury, and irreversible chronic scarring. Incorporation of these biomarkers into prospective transplant cohorts will be essential for biomarker qualification and treatment-response monitoring.

Lessons from native disease therapy and their applicability post-transplant

As understanding of the key upstream drivers of IgAN pathogenesis and downstream mechanisms of injury continues to grow, the therapeutic portfolio for native IgAN has expanded considerably, with an array of B-cell and plasma cell modulators either approved or in advanced stages of study [51, 58–61].

Systemic steroids remain an option for IgAN, but their safety profile continues to weigh the balance toward targeted-release budesonide for many patients. This concern is well illustrated by the TESTING trial, in which the original methylprednisolone dosing regimen (0.6–0.8 mg/kg/day) had to be reduced partway through the study (to 0.4 mg/kg/day) after an excess of serious infections, including deaths, emerged in the treatment arm. Even at the reduced dose, methylprednisolone significantly lowered the risk of the composite outcome of kidney function decline, kidney failure, or death due to kidney disease compared with placebo [62], and significantly reduced Gd-IgA1 levels [63]. A substantial component of pathogenic IgA production is thought to arise from dysregulated mucosal immune responses, particularly in the gut-associated lymphoid compartment, although circulating and bone-marrow plasma cells may also contribute. Therefore, a targeted-release steroid formulation, budesonide, has been developed to reduce systemic toxicity. Targeted-release budesonide was the first medication to receive FDA approval for the treatment of IgAN and is displacing the use of systemic steroids given its efficacy in proteinuria reduction, Gd-IgA1 reduction, and eGFR decline, alongside a more favorable safety profile compared to systemic corticosteroids [64].

The growing recognition of the importance of the complement system as an effector mechanism of injury in IgAN [65], has driven the use of complement directed therapy in IgAN. Iptacopan, a complement factor B inhibitor, significantly slowed kidney function decline in the APPLAUSE-IgAN trial, with an annualized total eGFR slope of −3.10 mL/min/1.73 m^2 with iptacopan compared with −6.12 mL/min/1.73 m^2 with placebo [66].

Notably, all of these pivotal trials excluded patients with recurrent post-transplant IgAN. As a result, no established guidelines exist for treating recurrence, and experience with both newer agents and older immunosuppressants such as cyclophosphamide remains largely anecdotal. Registry data indicate that most patients diagnosed with recurrence are managed with supportive care directed at non-specific drivers of nephron loss, such as angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), with only a minority started on additional immunosuppression [12]. It is worth noting that this registry data predate the modern treatment paradigm for native IgAN, which now favors earlier initiation of disease-specific therapy alongside supportive care with ACE inhibitors, ARBs, or sodium-glucose cotransporter 2 (SGLT2) inhibitors.

Experience in using targeted-release budesonide in treating post-transplant IgAN is largely limited to case reports and small case series [67, 68]. In these reports, targeted-release budesonide slowed eGFR decline and significantly reduced proteinuria, and appeared reasonably well tolerated; hyperglycemia and fluid overload were reported but did not lead to treatment discontinuation. Notably, none of these patients had changes made to their maintenance immunosuppression, and low-dose systemic prednisone was continued alongside targeted-release budesonide. To our knowledge, the largest reported experience comes from a cohort of 10 patients treated at the University of Parma, Italy. In this cohort, investigators observed no meaningful reduction in proteinuria or improvement in eGFR; it is important to note, however, that the formulation used differed from that studied in the NEFIGARD trial, employing a controlled-release budesonide formulation typically used to treat inflammatory bowel disease [69].

Experience with iptacopan in post-transplant IgAN recurrence is similarly confined to case reports and small case series. In one report, iptacopan was used in a patient with recurrence refractory to aggressive immunosuppression, including rituximab, cyclophosphamide, and systemic steroids; after this therapeutic failure, with active crescentic IgAN on biopsy, the patient was started on iptacopan with penicillin prophylaxis, and a follow-up biopsy at 48 months post-transplant showed features of chronic injury but resolution of active inflammatory activity [70]. A separate case series of three patients treated with iptacopan alongside a short course of high-dose prednisone showed significant proteinuria reduction in two of the three [71]. A larger case series of five patients offered a more tempered picture: iptacopan produced a marked reduction in glomerular C5b-9 and C3 deposition on repeat biopsy within 6–12 months, but this histologic response was not consistently accompanied by proteinuria improvement, suggesting complement blockade may attenuate ongoing immune-mediated injury without necessarily producing an early clinical response [72]. Across these reports, no patients underwent changes to their maintenance immunosuppression, and all received meningococcal vaccination with penicillin prophylaxis during treatment given the risk of attenuated vaccine responses; no infections were observed during follow-up, though follow-up duration was short at the time of publication.

Telitacicept, a TACI-Ig fusion protein targeting both BAFF and APRIL, has generated the most substantial post-transplant recurrence data among B-cell/plasma cell-directed therapies to date, from two recent cohorts in China. In a retrospective series of 10 patients with biopsy-proven recurrent IgAN treated with telitacicept (160–240 mg weekly, subcutaneously), 6 months of therapy produced complete remission in two patients and partial remission in two more, with a proteinuria reduction exceeding 30% in 60% of patients overall; renal function remained stable in nine of ten patients through 12 months. Safety was reassuring on the whole, with no deaths, no serious adverse events, and no progression to graft failure or ESKD, though one patient (10%) developed

TABLE 2 Targeted therapies for IgAN: Mechanism, regulatory status, and availability of post-transplant recurrence evidence.

Drug/Class	Four-hit target	Regulatory status (native IgAN)	Key native-disease evidence	Post-transplant recurrence evidence	Notable safety signal in transplant recipients
Targeted-release budesonide	Hits 1–2 (mucosal B-cell/IgA production)	FDA approved EMA approved	NEFIGARD phase 3: sustained eGFR benefit at 2 years [64]	Case reports (proteinuria reduction, eGFR stabilization) [67, 68]; 10-patient Parma cohort showed no benefit (different, IBD-type formulation used).	Hyperglycemia, fluid overload reported; no treatment discontinuations
Systemic corticosteroids	Hits 1–4 (broad immunomodulation)	No IgAN-specific approval	TESTING trial: reduced composite kidney outcome vs. placebo [62].	Registry-level association only (ANZDATA, UNOS/OPTN); no dedicated interventional data [19, 20]	Dose-dependent serious infection risk (TESTING); compounds with baseline transplant immunosuppression
Iptacopan *(complement factor B inhibitor)*	Hit 4 (alternative complement pathway)	FDA approved Not approved by EMA	APPLAUSE-IgAN: annualized eGFR slope −3.10 vs. −6.12 mL/min/1.73m^2 [66].	1 case report (refractory crescentic recurrence, resolved activity) [70]; 3-patient series (2/3 responded) [71]; 5-patient series (histologic response without consistent proteinuria improvement) [72].	Meningococcal vaccination + penicillin prophylaxis required; no infections in small series (short follow-up)
Sparsentan *(dual endothelin-A/AT1 antagonist)*	Hit 4	FDA approved EMA approved	PROTECT trial: sustained eGFR benefit at 2 years, +3.8 mL/min/1.73m^2 vs. placebo [75].	Case reports show proteinuria reduction; one report describes *de novo* rather than confirmed recurrent disease [76, 77].	Limited transplant-specific safety data
Atrasentan *(selective endothelin-A antagonist)*	Hit 4	FDA accelerated approval. Not approved by EMA	ALIGN trial: sustained eGFR benefit at 2.5 years, 2.6 mL/min/1.73 m^2 [78].	None identified	N/A
Sibeprenlimab *(anti-APRIL monoclonal antibody)*	Hit 1 (APRIL neutralization)	FDA accelerated approval* (nov 2025) Not approved by EMA	Phase 3 interim: proteinuria reduction −50.2% vs. placebo [51].	None identified	N/A
Atacicept *(dual BAFF/APRIL inhibitor, TACI-Ig)*	Hit 1 (BAFF + APRIL blockade)	FDA accelerated approval (Jul 2026) Not approved by EMA	Phase 3 interim: proteinuria reduction −45.7% vs. −6.8% placebo [79].	None reported yet; basket trial enrolling recurrence (PIONEER, NCT06983028)	N/A
Telitacicept *(dual BAFF/APRIL inhibitor, TACI-Ig)*	Hit 1 (BAFF + APRIL blockade)	Approved in China; not yet FDA or EMA approved	Phase 3 (Stage A): proteinuria reduction −55% vs. placebo [60].	Most substantial evidence to date: 10-patient retrospective cohort (CR/PR achieved, stable renal function) + 25-patient prospective cohort (UPCR/UACR reduced 51.6%/62.7% at week 28) [73, 74].	1 antibody-mediated rejection event (10%) in the 10-patient cohort; hyperuricemia common

Abbreviations: ANZDATA, australia and new zealand dialysis and transplant registry; APRIL, a proliferation-inducing ligand; AT1, angiotensin II, type 1 receptor; BAFF, B-cell–activating factor; CR, complete remission; eGFR, estimated glomerular filtration rate; EMA, european medicines agency; FDA, U.S., food and drug administration; IBD, inflammatory bowel disease; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; N/A, not applicable; OPTN, organ procurement and transplantation network; PR, partial remission; TACI-Ig, transmembrane activator and calcium-modulating cyclophilin ligand interactor–immunoglobulin fusion protein; UACR, urine albumin-to-creatinine ratio; UNOS, united network for organ sharing; UPCR, urine protein-to-creatinine ratio.* Accelerated FDA, Approval; FDA, pathway that lets a drug reach the market based on a surrogate endpoint, e.g., proteinuria reduction in IgAN.

antibody-mediated rejection after 12 months of treatment [73]. A larger, prospective single-arm cohort of 25 transplant recipients with biopsy confirmed recurring IgAN receiving add-on telitacicept reported substantial reductions in 24-h urinary protein and urine albumin-to-creatinine ratio by week 28 (51.6% and 62.7%, respectively; both $p < 0.001$) [74]. Together, these early data position telitacicept as a promising approach to the B-cell/plasma cell-driven biology underlying IgAN recurrence, though controlled trials and longer safety follow-up, particularly around alloimmune risk, are still needed. List of available therapies for IgAN, along with the corresponding evidence for their use in post-transplant recurrence, are summarized in Table 2.

In current clinical practice, treatment decisions should remain individualized. Before escalation of disease-specific therapy, clinicians should exclude competing causes of proteinuria, optimize supportive measures including blood pressure control, renin-angiotensin system blockade and SGLT2 inhibition when appropriate, and carefully assess concomitant alloimmune injury on biopsy. Disease-specific therapies should ideally be administered within prospective clinical studies whenever feasible.

Conclusions and future directions

Recurrent IgAN after kidney transplantation is an important cause of late allograft injury. Its impact is underestimated because recurrence may be histologically silent, diagnosed years after transplantation, and confounded by other causes of late graft dysfunction, including chronic antibody-mediated rejection, calcineurin inhibitor toxicity, and chronic scarring. As allograft survival improves, progressive recurrent IgAN may increasingly contribute to late graft loss.

Progress in this area will require a transplant-specific evidence base. Harmonized multicenter registries should capture not only recurrence rates, but also biopsy indication, time from transplant to recurrence, proteinuria and eGFR trajectories, DSA status, rejection history, induction and maintenance immunosuppression, steroid exposure, and standardized histologic features of activity and chronicity. The TANGO consortium [80] already provides a model for this type of collaborative effort; the next step is to expand and standardize such registries so that clinically meaningful recurrence can be distinguished from incidental mesangial IgA deposition.

Trials of newer IgAN therapies have consistently excluded transplant recipients: potential drug-drug interactions with calcineurin inhibitors, concerns about compounding infection risk on top of maintenance immunosuppression, and the practical difficulty of powering a trial against a hard endpoint like graft loss that may take a decade or more to accrue have all made this a difficult population to study. Future studies should be designed around the realities of transplant nephrology. Graft loss is an important outcome, but it is impractical as the primary endpoint for most trials of recurrent IgAN. More feasible studies should use enrichment strategies and short-to intermediate-term endpoints, including change in proteinuria, eGFR slope, histologic activity and chronicity, complement deposition, and patient-centered safety outcomes. Trials should stratify by DSA and antibody-mediated rejection status, induction and maintenance immunosuppression, steroid exposure, time from transplant to recurrence, and the presence of active versus chronic lesions. Basket or platform designs that include transplant recipients alongside native IgAN cohorts may be an efficient first step, but dedicated transplant cohorts will ultimately be needed to define dosing, safety, and efficacy.

Biomarker development should be embedded in these studies rather than pursued separately. Serial assessment of Gd-IgA1, anti-glycan antibodies, BAFF/APRIL levels, complement biomarkers, urine markers, and tissue readouts may help identify patients at risk, monitor response, and separate active recurrence from irreversible chronic injury. At present, none of these tools is sufficiently validated to guide routine post-transplant management, but they should be incorporated prospectively into registries and trials.

In the era of targeted IgAN therapies, kidney transplant recipients should not remain therapeutic orphans. The next step is a transplant-specific evidence base that moves beyond anecdotal add-on therapy and defines rational, safe, and measurable treatment strategies for recurrent IgAN before irreversible allograft injury develops.

Author contributions

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