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REVIEW

Post-transplant IgA nephropathy: a rapidly evolving field of kidney transplant medicine

Mehmet Kanbay[1] · Lasin Ozbek[2] · Mustafa Guldan[2] · Sidar Copur[3] · Jonathan Barratt[4,5]

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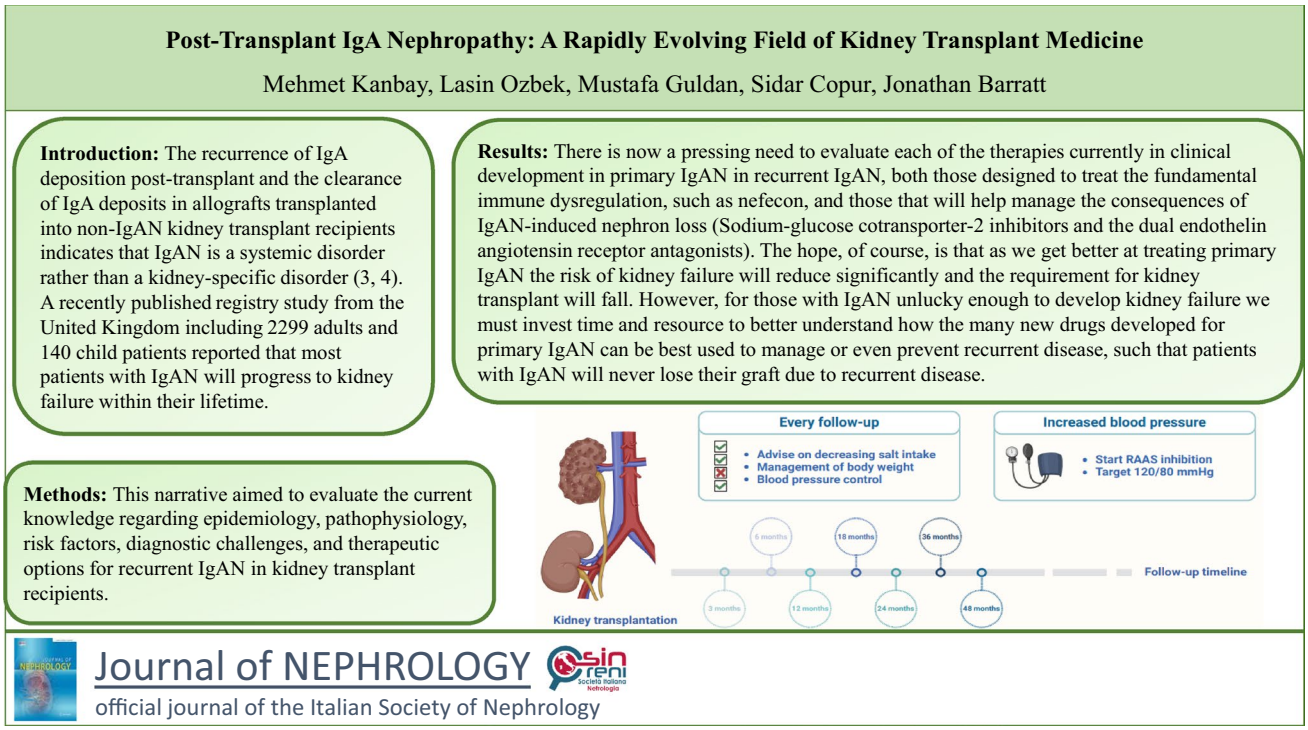
Abstract

IgA nephropathy is the commonest pattern of primary glomerular disease in the world, with high rates of progression to kidney failure. As IgA nephropathy commonly causes kidney failure at a young age, kidney transplantation is commonly used to treat kidney failure. However, high rates of recurrent disease in the allograft remain a common management challenge. The prevalence of post-transplant recurrence approaches 15% at ten years post-transplant and is associated with poor allograft function and high rates of allograft loss. Post-transplant IgA nephropathy has also been described de novo in some case series. Treatment of recurrent IgA nephropathy has been challenging but with the rapid growth of new treatments for IgA nephropathy it is likely that many of these treatments will, over time, transition to the treatment of recurrent disease. In this narrative review, our aim is to evaluate post-transplant IgA nephropathy in terms of epidemiology, risk factors, underlying pathophysiology, diagnosis and management strategies.

Graphical abstract



Keywords Kidney transplantation · IgA nephropathy · Recurrence · Sodium-glucose cotransporter-2 inhibitors · Angiotensin converting enzyme inhibitors · Angiotensin receptor blockers

Extended author information available on the last page of the article

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Introduction

IgA nephropathy (IgAN), first described in 1968 by Berger et al., is the most common primary glomerular disease in the world, with an incidence of 2–10 per 100,000 person-years, and it has a broad geographical distribution [1]. Even though the exact underlying pathophysiology is unclear, the primary hypothesis involves IgA immune complex formation driven by high serum levels of galactose-deficient IgA1 and IgA-reactive IgA and IgG antibodies [2]. The recurrence of IgA deposition post-transplant and the clearance of IgA deposits in allografts transplanted into non-IgAN kidney transplant recipients indicates that IgAN is a systemic disorder rather than a kidney-specific disorder [3, 4]. A recently published registry study from the United Kingdom including 2299 adults and 140 children reported that most patients with IgAN will progress to kidney failure within their lifetime [5]. Studies reporting on the incidence of IgAN transplant recurrence have reported variable incidence rates, impact on allograft function and risk factors for recurrence. Treatment of recurrence is equally variable [6, 7]. In this narrative review, our aim is to evaluate the current knowledge regarding epidemiology, pathophysiology, risk factors, diagnostic challenges, and therapeutic options for recurrent and de novo IgAN in kidney transplant recipients.

Recurrent IgA nephropathy after kidney transplantation

Long-term data regarding the recurrence of primary glomerular diseases in terms of prevalence, risk factors, clinical outcomes and therapeutic approaches are limited. An analysis of the 2002 Australia and New Zealand Dialysis and Transplant (ANZDATA) revealed that 8.4% (95% CI 5.9–12.0) of all allograft failures at 10 years post-transplant were due to the recurrence of glomerular disease [8]. While recurrence of primary focal and segmental glomerulosclerosis (Hazard Ratio [HR] 2.0, 95% Confidence Interval [CI] 1.18–3.41; p value = 0.01) and mesangiocapillary glomerulonephritis type I (predominantly C3 glomerulopathy, HR 2.63, 95% CI 1.39–4.98; p value = 0.003) are traditionally thought of as the most likely primary glomerular diseases to recur, similar rates of allograft failure among patients with IgAN were also reported in this ANZDATA analysis (HR 0.78, 95% CI 0.45–1.34; p value = 0.36) [8]. By contrast, another large-scale population-based study utilizing data from the US Renal Data System (USRDS) 2017 report identified IgAN as the primary glomerular disease with the lowest risk for allograft failure or mortality during a median of 5.5 years of follow-up [9]. This probably reflects the slow rate of IgAN recurrence with greater allograft dysfunction likely becoming apparent over a longer follow-up period. Consistent with a more prolonged disease trajectory, a single-center retrospective cohort study including 190 kidney transplant recipients with IgAN and 380 non-diabetic controls reported a lower death-censored graft survival (72.4% vs. 62.6%, p value = 0.038) and higher rates of allograft failure (p value = 0.025) in the IgAN cohort at 15-year follow-up [10]. Analysis of 2017 ANZDATA registry data demonstrated gradually increasing rates of IgAN recurrence with time post-transplant, with an incidence of 5.1%, 10.1% and 15% at 5, 10 and 15-year follow-up [11]. IgAN recurrence was associated with higher rates of allograft failure (adjusted HR [aHR] 2.04; 95% CI 1.81–2.31) and a 42% allograft loss within five years of diagnosis. In a separate study of 1965 kidney transplant protocol and clinically-indicated allograft biopsies from the Mayo Clinic in the United States, with a median follow-up of 86 months, histopathological recurrence occurred in 12.5%, 42.0% and 51% of IgAN patients at 1-year, 3-year and 5-year follow-up, respectively [12]. In this study, IgAN recurrence was associated with a higher risk of death-censored allograft failure (aHR 3.44, 95% CI 1.22–9.71). To conclude, recurrence of IgAN is a common occurrence and is associated with an appreciable allograft failure rate over time.

Our current understanding of the pathogenesis of IgAN is that it is a systemic disease characterized by the presence of circulating IgA immune complexes which have a propensity to accumulate in the glomerular mesangium, where they trigger glomerular injury, scarring and ultimately nephron loss and kidney failure. The major substrate for IgA immune complex formation is the presence in the circulation of excess quantities of a set of IgA1 *O*-glycoforms that carry fewer galactose residues at the IgA1 hinge region (Fig. 1). These IgA1 *O*-glycoforms are collectively termed Gd-IgA1 and can be measured in the serum using a number of different research-only assays. These IgA1 *O*-glycoforms are prone to self-aggregation and aggregation with a number of different serum proteins and IgA and IgG antibodies that recognize the *N*-acetylgalactosamine residues at the IgA1 hinge region that have been exposed by a lack of bound galactose. These IgA and IgG antibodies are likely "normal" antibodies that have developed in response to microbial pathogen exposure, with specificity for bacterial cell wall glycoproteins, and by chance, cross react with these IgA1 *O*-glycoforms. This is unlike what occurs in diseases such as ANCA-associated vasculitis, membranous nephropathy and systemic lupus erythematosus, where there is loss of self-tolerance and clonal expansion of autoreactive B cells. In addition, there is convincing evidence that the "pathogenic" forms of IgA1 are derived from the mucosal immune

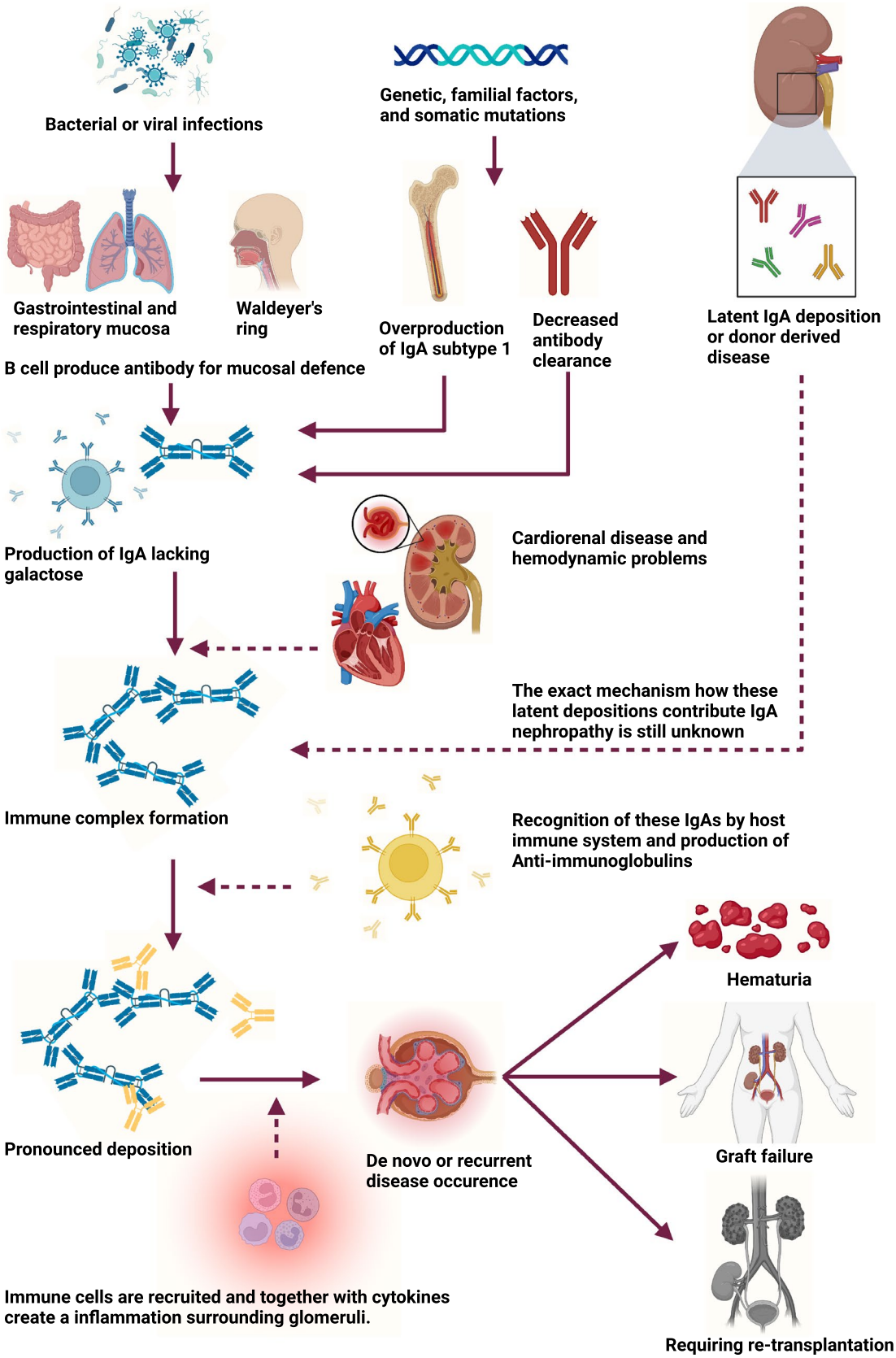

Fig. 1 The hypothetical underlying pathophysiology of post-transplant IgA nephropathy

system, and in particular the gut-associated lymphoid tissue, in contrast to diseases like ANCA-associated vasculitis, membranous nephropathy and systemic lupus erythematosus where the autoreactive B cell clones reside within central lymphoid sites such as the bone marrow, spleen and central lymph nodes. This mucosal link was reinforced during the COVID-19 pandemic, when a surge in reported cases of IgAN and IgA vasculitis exacerbations were reported [13, 14]. In healthy individuals the mucosal IgA1 response is tightly regulated with little spillover of mucosal IgA into the systemic circulation, however, in IgAN the mucosal response is dysregulated and exaggerated, leading to an increase in mucosal Gd-IgA1 in the circulation, which in turn promotes immune complex formation [15, 16]. The most recent meta-genome-wide association study identified over 30 different genetic risk alleles for the development of IgAN, many of which are involved in regulating the mucosal immune system response and mucosal health [17].

These pathogenic differences between IgAN and "traditional" autoimmune diseases like ANCA-associated vasculitis, membranous nephropathy, and systemic lupus erythematosus, likely underlie the lack of response seen in IgAN to traditional immunosuppressants used to treat autoimmune disease (and prevent kidney transplant rejection and IgAN recurrence) such as rituximab, cyclophosphamide, mycophenolate mofetil, calcineurin inhibitors and systemic glucocorticoids, as the pathogenic IgA-producing cells are located in a relatively protected immune microenvironment. Specific approaches are required to target these pathogenic IgA producing cells, and over the last 3–5 years we have seen great advances in IgAN therapies, including gut-directed therapies which will be discussed later.

It is, therefore, not surprising that transplanting a new kidney into a patient with IgAN will expose the new kidney to the same immune complex burden with a consequent risk of recurrent disease. Understanding that there are high rates of histopathological recurrence and consequent allograft dysfunction among IgAN kidney transplant recipients, it is important to delineate the potential factors pre-transplant that increase the risk of recurrent disease (Table 1). A multicenter retrospective cohort study including 504 kidney transplant recipients with IgAN evaluated the prevalence and risk factors for IgAN recurrence after transplantation [7]. Recurrent IgA deposition occurred in 16.2% of allograft biopsies over a median of 8.7 years of follow-up, with gradually increasing rates with longer follow-up periods, reaching a recurrence rate of 23% at fifteen years. Most cases were diagnosed through clinically indicated allograft biopsies (95%) in response to asymptomatic elevations of serum creatinine, hematuria or proteinuria, rather than protocol biopsies (5%). Lower median age at kidney transplantation (41 vs 46; p value = 0.002), lower time interval between the diagnosis of IgAN and kidney failure 48 vs. 72 months; p value = 0.04), higher rates of donor specific antibodies (DSAs) (8% vs. 3%; p value = 0.03) and pre-emptive kidney transplantation (30% vs. 16%; p value = 0.002) were independently associated with a higher risk of recurrent IgAN. IgAN recurrence was associated with allograft survival rates

Table 1 Risk Factors for IgA Nephropathy and Post-Transplant Recurrence

General Risk Factors for IgA Nephropathy
Genetic Predisposition
High Serum Levels of IgA
Galactose-Deficient IgA1-specific IgG Antibodies
Mucosal Immune System Abnormalities
Environmental Triggers (e.g., infections, pollutants)
Risk Factors for Post-Transplant IgAN Recurrence
Lower Age at Kidney Transplantation
Shorter Interval Between IgAN Diagnosis and Kidney Failure
Higher Donor-Specific Antibodies
Pre-emptive Kidney Transplantation
Living Donor
Younger Donor Age
Lower Degree of HLA-Mismatch
Shorter Time on Dialysis
Higher Serum Levels of IgA or Galactose-Deficient IgA1-specific IgG Antibodies
Acute and/or Chronic Rejection Episodes
Immunosuppressive Regimen
Corticosteroid Therapy Withdrawal

of 94% at 1 year, 83% at 5 years and 68% at 8 years after the diagnosis, while the most common causes of allograft loss included recurrent IgAN alone (44%), recurrent IgAN combined with chronic rejection or unknown causes.

In other smaller studies, donor type, DSA titers, acute and/or chronic rejection episodes, infectious diseases, immunosuppressive regimens, younger age at kidney transplantation [18–22], higher pre- and post-transplant serum levels of Gd-IgA1 and galactose-deficient IgA1-specific IgG antibodies pre-transplantation [23, 24], rapid progression of IgAN to kidney failure [18, 25], shorter time on dialysis and pre-emptive kidney transplantation [26] have all been identified as significant recipient-related risk factors for recurrent IgAN. Analysis of the ANZDATA Registry showed an approximate 2% risk reduction for IgAN recurrence with every one-year increase in recipient age at transplantation [11], and a significant increase in risk with shorter interval between IgAN diagnosis and development of kidney failure (mean difference: – 1.84 years, 95% CI – 2.43 to – 1.25) and dialysis duration (mean difference: – 3.14 months, 95% CI – 4.18 to – 2.09). Consistently reported donor-related risk factors include living donor, related donor, younger age of donor and lower degree of HLA-mismatch. By contrast, transplantation-related risk factors, including shorter cold ischemia time and immunosuppressive regimen, have not been consistently reported as risk factors across clinical studies [26, 27]. With regard to immunosuppressive regimens, one area of debate is the impact of corticosteroid therapy withdrawal on risk of IgAN recurrence [20, 28–30]. A retrospective analysis of the United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN), including 9690 kidney transplant recipients with IgAN and a median follow-up of 5.64 years, evaluated the impact of early corticosteroid withdrawal on the risk of IgAN recurrence. A total of 191 patients experienced graft loss due to IgAN recurrence. Maintenance corticosteroid therapy, compared to early corticosteroid withdrawal, was associated with lower IgAN recurrence risk (20.54% vs. 13.82%, HR 0.695, 95% CI, 0.511–0.945; *p* value: 0.02) but a higher risk of graft loss due to acute rejection (16.79% vs. 13.13%) and chronic allograft nephropathy (37.83% vs. 28.28%) [31]. Consistent with these findings, an analysis of 1521 patients in the ANZDATA registry demonstrated a similar protective effect of corticosteroid maintenance therapy (HR 0.50, 95% CI 0.30–0.84) [32]. These observations have, however, not been confirmed in other retrospective studies [7]. There is equal uncertainty regarding the impact of other maintenance immunosuppressive regimens, such as mycophenolate mofetil, on the risk of recurrence [33–37].

One group of patients that appear at high risk of recurrent disease are those who develop a rapidly progressive form of IgAN, which is invariably associated with extensive crescent formation and responds poorly to currently available treatment [38]. In a study from China, rapidly progressive IgAN with crescents was associated with very poor outcomes in both native kidneys and the corresponding allografts [39].

The currently accepted pathogenic model of IgAN focuses on the formation of IgA immune complexes in the circulation, that over time accumulate in the glomerular mesangium. The substrate for immune complex formation is a persistent increase in the circulatory levels of poorly *O*-galactosylated IgA1 glycoforms (commonly measured as galactose-deficient IgA1) (Fig. 1) [40]. A prospective observational study involving a total of 38 kidney transplant recipients reported that the pre-transplant levels of galactose-deficient IgA1 and the IgA and IgG antibodies that recognize these IgA1 *O*-glycoforms were predictive for IgAN recurrence [23]. A similar association was reported in a study involving 27 kidney transplant recipients in whom galactose-deficient IgA1 levels measured post-transplant were also predictive of recurrence (area under the curve [AUC] 0.76; 95% CI 0.57–0.95, $p = 0.02$) [24]. These data support the further evaluation of galactose-deficient IgA1 as a biomarker of disease activity and risk of transplant recurrence.

Developing therapeutic options

Therapeutic options for IgAN are rapidly evolving but have traditionally focused on lifestyle modification, blood pressure control and limiting proteinuria with renin–angiotensin–aldosterone system (RAAS) inhibitors [41, 42]. Treatments directed at the fundamental immunology of IgAN, that is treatments to reduce or prevent IgA immune complex formation, have until recently been an aspiration rather than a reality. Systemic glucocorticoids have been used to manage the inflammatory consequences of immune complex deposition, but due to their significant toxicity and poor tolerability, they are variably used in clinical practice (Fig. 2).

Over the past five years a number of new treatments have become available to help manage the consequences of IgAN-induced nephron loss. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors such as dapagliflozin and empagliflozin, and the dual endothelin angiotensin receptor antagonist (DEARA) sparsentan have been shown to improve proteinuria reduction and reduce the rate of loss of eGFR in patients with IgAN above that achieved with RAAS inhibitors alone in patients with biopsy-proven primary IgA and proteinuria of at least 1·0 g/day despite maximized RAAS inhibition [43, 44]. As an alternative to systemic glucocorticoids, multiple complement system inhibitors are beginning to show promise as an effective way to reduce glomerular inflammation in studies in IgAN. The factor B small molecule inhibitor iptacopan was recently approved by the Food and

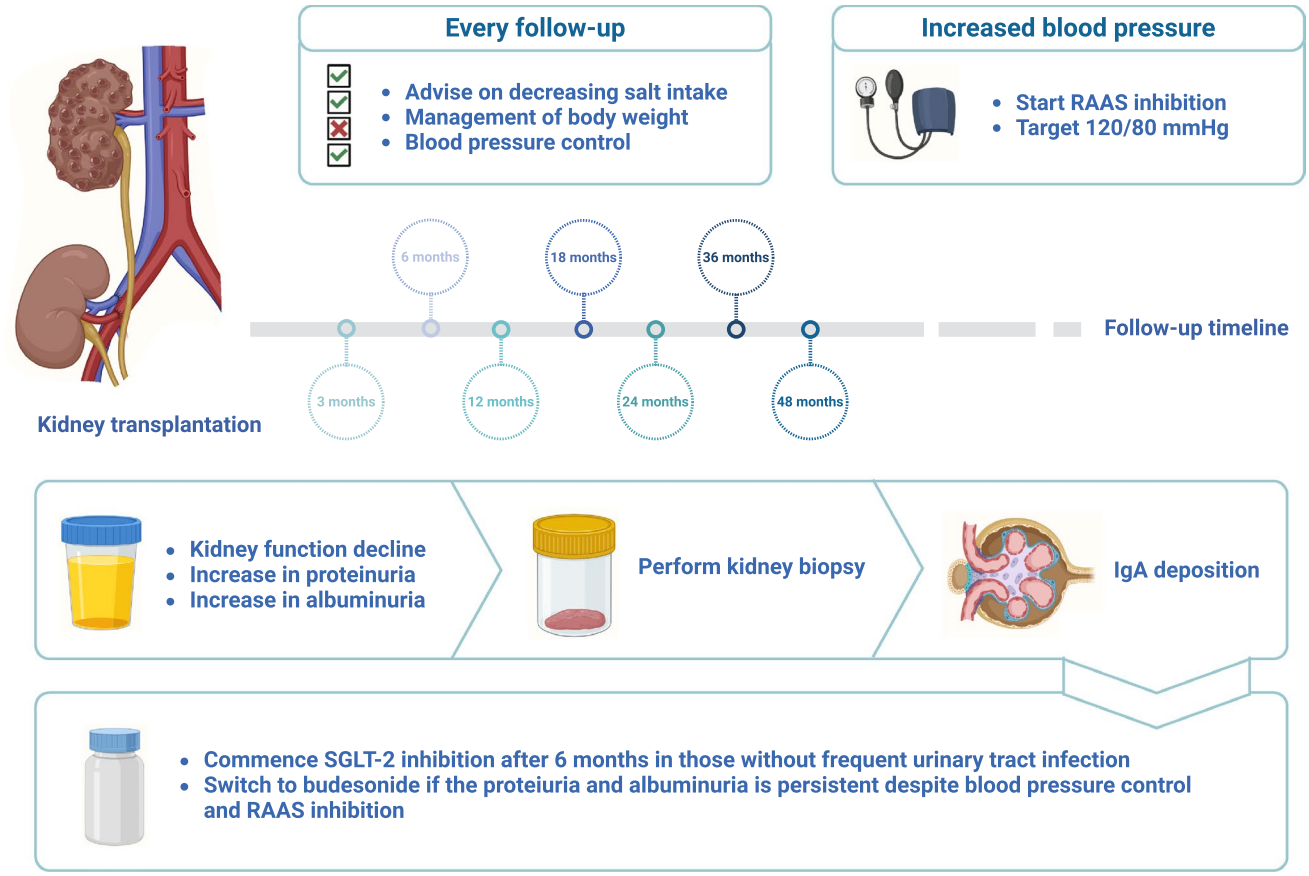

Fig. 2 Suggestion for following and managing IgA nephropathy after kidney transplantation

Drug Administration (FDA) in the United States for use in IgAN, and it is the first complement inhibitor available for IgAN [45]. Phase 2 studies of C5 inhibition with cemdisiran [46] and ravulizumab [47] have reported positive findings in IgAN, with use of both drugs associated with a reduction in proteinuria and the rate of loss of kidney function. A factor B antisense oligonucleotide is currently being evaluated in the phase 3 Imagination study, and ravulizumab is being studied in the phase 3 ICAN study [47]. There are also early phase studies of complement inhibitors targeting C3 and factor D. But perhaps most transformative are the agents that are directed at reducing the synthesis of pathogenic forms of IgA and circulating IgA immune complex formation (NCT06564142, NCT05248659). Nefecon, a specific formulation of budesonide, designed to reduce mucosal IgA production in the terminal ileum has been shown in the phase 2 NEFIGAN and phase 3 NefIgArd studies to reduce proteinuria, slow the rate of loss of eGFR and impact positively on multiple pathogenic pathways in IgAN [48–50]. Similarly, there are consistent data from trials of drugs targeting the two key cytokines that regulate B cell and plasma cell survival and proliferation; a proliferation-inducing ligand (APRIL) and B cell activating factor (BAFF), that by blocking these cytokines, reduce pathogenic forms of IgA, reduce proteinuria, and slow the rate of loss of kidney function [51] (Fig. 3).

Despite these advances in the management of IgAN in native kidneys, there are no data regarding the utility of these new agents in kidney transplantation. The only data that are available concern general supportive care measures. A study involving 21 post-transplant IgAN and 63 primary IgAN patients demonstrated similar beneficial effects, in terms of proteinuria and blood pressure management, of RAAS inhibitors in subjects with recurrent disease as has been well documented in patients with primary IgAN [52]. In another retrospective single-center study including 75 cases of biopsy-proven recurrent IgAN, there was a numerically higher graft survival at 5- (92.9 vs 86.5%; p value = 0.34) and 10-year follow-up (81.6 vs 72.7%; p value = 0.32) for those patients who were treated with RAAS inhibitors [53]. By contrast, a study of 47 recurrent IgAN cases reported no effect of either RAAS inhibitors or maintenance immunosuppressive regimens on allograft function or survival [54].

As in native disease, the use of systemic glucocorticoids in recurrent IgAN is controversial. While there is some evidence to suggest that early withdrawal of maintenance

Post-Transplant IgA Nephropathy: What Is The Evidence?

Recipient-Related Factors:

- ✓ Younger age at transplantation
- ✓ Male gender
- ✓ Shorter duration in-between IgA nephropathy diagnosis to ESKD
- ✓ Longer time on hemodialysis
- ✓ Higher serum galactose-deficient IgA1 levels at transplantation
- ✓ Higher serum levels of autoantibodies for galactose-deficient IgA1
- ✓ Certain HLA types (HLA-B46, HLA-B35, HLA-DR4 etc.)
- ✓ Pre-emptive kidney transplantation

Donor-Related Factors:

- ✓ Younger age at transplantation
- ✓ Living-related donors
- ✓ Higher rates of HLA mismatch

Therapy-Related Factors:

- Lack of induction therapy with anti-IL2 receptor antibodies (ie. Basiliximab)
- Early withdrawal of corticosteroid maintenance therapy
- mTOR inhibitor therapy in maintenance regimen
- Lack of MMF in maintenance regimen

What Do We Know?

- ✓ IgA nephropathy has high rates of post-transplant recurrence reaching up to 15% over ten-year follow-up.
- ✓ Post-transplant IgA nephropathy is not a benign process with considerable detrimental effects on graft survival and function.
- ✓ Post-transplant IgA nephropathy may occur as a recurrence of primary disease.
- ✓ Diagnosis of post-transplant IgA nephropathy depends upon histopathological examination.

What to Expect in the Future?

- ✓ There is currently no data on various therapeutic alternatives in the management of post-transplant IgA nephropathy including:
  - SGLT-2 inhibitors (ie. Empagliflozin, Dapagliflozin)
  - Endothelin receptor antagonists (ie. Sparsentan)
  - Complement targeting agents (ie. Avacopan, Ravulizumab)
- ✓ There is currently no predictive factor for post-transplant IgA nephropathy.
- ✓ There is currently no preventive measure for post-transplant IgA nephropathy.

Fig. 3 Post-transplant IgA nephropathy-related risk factors and current state of scientific knowledge. *Ig* Immunoglobulin, *ESKD* End stage kidney disease, *HLA* Human leukocyte antigen, *mTOR* Mammalian target of rapamycin, *MMF* Mycophenolate mofetil, *IL* Interleukin, *SGLT* Sodium glucose cotransporter

corticosteroid therapy is associated with a higher risk of recurrent disease and allograft loss, this has not been uniformly reported across case series. With respect to the use of systemic glucocorticoids to manage recurrent IgAN, there are few data. In a single-center retrospective study, methylprednisolone 500 mg/day intravenously for three consecutive days in months 1–3–5 followed by 0.5 mg/kg/day per oral dose for a total of six months compared to supportive therapy alone was associated with a lower degree of proteinuria (0.9 vs. 1.9 g/day; p value = 0.04) and lower serum creatinine measurement (1.8 ± 0.4 vs. 2.7 ± 0.9 mg/dl; p value = 0.002) [55], however, follow up was short and long term outcomes are not known. Similarly, treatments that have failed to show benefit in randomized controlled clinical trials in primary IgAN, such as rituximab and tonsillectomy, have been tried in recurrent disease but data are limited to case reports and cannot inform treatment decisions [39, 56–58].

There is now a pressing need to evaluate the therapies currently in clinical development in primary IgAN and recurrent IgAN, both those designed to treat the fundamental immune dysregulation, such as Nefecon, and those that will help manage the consequences of IgAN-induced nephron loss (SGLT-2 inhibitors and the dual endothelin angiotensin receptor antagonists). The hope, of course, is that as we get better at treating primary IgAN the risk of kidney failure will decrease significantly as will the need for kidney transplant. However, for those with IgAN unlucky enough to develop kidney failure we must invest time and resources to better understand how the many new drugs developed for primary IgAN can be best used to manage or even prevent recurrent disease, such that patients with IgAN will never lose their graft due to recurrent disease. Until those studies are performed it would seem appropriate to treat recurrent IgAN in the same way as described in the recently updated KDIGO Clinical Practice Guidelines for IgA nephropathy in the native kidneys [59].

Future directions

Future directions (Table 2) in the management of IgAN, particularly in the post-kidney transplantation setting, should adopt a comprehensive strategy to optimize treatment efficacy and reduce recurrence rates. Key areas of focus include the evaluation of SGLT-2 inhibitors. If these agents demonstrate effectiveness, determining the appropriate timing for their initiation will be essential to achieve maximal therapeutic benefit. Additionally, defining the

Table 2 Therapeutic Frontiers and Research Recommendations

Future direction	Description
SGLT2 Inhibitors	Evaluate the efficacy of SGLT2 inhibitors and determine the optimal timing for initiation
Optimal Blood Pressure Target	Define the ideal blood pressure target (e.g., 120/80 mmHg) and assess its impact on long-term outcomes
Alternative Immunosuppressants	Investigate alternatives to traditional corticosteroids, such as Nefecon or budesonide, for fewer side effects
Timing of RAAS Inhibitors	Determine the best timing for initiating Renin–Angiotensin–Aldosterone System (RAAS) inhibitors
Endothelin Receptor Antagonists	Explore the efficacy of endothelin receptor antagonists in managing IgAN
Complement Pathway Inhibitors	Assess the potential of drugs targeting the alternative complement pathway, such as those inhibiting APRIL
Emerging Agents	Investigate newer agents like TGF-beta inhibitors or anti-fibrotic drugs for innovative treatment strategies

optimal blood pressure target for IgAN patients, ideally 120/80 mmHg, remains critical; however, further research is needed to establish its impact on long-term outcomes. The exploration of alternative immunosuppressants, such as Nefecon or budesonide, could provide an advantageous profile compared to traditional corticosteroids like methylprednisolone. Specifically, research into the use of budesonide, which has been shown to suppress mucosal IgA secretion, may offer beneficial effects in this patient group. Moreover, assessing the role of RAAS inhibitors and identifying the optimal timing for their administration could be crucial in mitigating IgAN recurrence. Investigating novel therapies, including endothelin receptor antagonists, is warranted to evaluate their efficacy in managing the disease. Additionally, targeting the alternative complement pathway with agents that inhibit APRIL or complement activation may open new therapeutic avenues (Fig. 3). The potential of emerging agents, such as TGF-beta inhibitors or anti-fibrotic drugs, should also be explored to identify innovative strategies for preventing disease progression.

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Declarations

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Not applicable.

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Authors and Affiliations

Mehmet Kanbay[1] · Lasin Ozbek[2] · Mustafa Guldan[2] · Sidar Copur[3] · Jonathan Barratt[4,5]

✉ Mehmet Kanbay
mkanbay@ku.edu.tr

[1] Division of Nephrology, Department of Internal Medicine, Koc University School of Medicine, 34010 Istanbul, Turkey

[2] Department of Medicine, Koc University School of Medicine, Istanbul, Turkey

[3] Division of Internal Medicine, Department of Internal Medicine, Koç University School of Medicine, Istanbul, Turkey

[4] Mayer IgA Nephropathy Laboratories, Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

[5] John Walls Renal Unit, University Hospitals Leicester NHS Trust, Leicester, UK