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RESEARCH ARTICLE

Arab Renal Care Group Protocol: Outcomes of a Preventive Immunomodulatory Strategy in Low- to Moderate-Risk Living-Related Kidney Transplant Recipients With Uncertain Primary Renal Disease

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ABSTRACT

Background: Recurrent glomerular disease and acute rejection remain significant contributors to kidney allograft dysfunction. Standard immunologic risk stratification tools primarily focus on alloimmune mechanisms and may underestimate non–human leukocyte antigen–mediated pathways in recipients with uncertain or immune-mediated primary renal disease.

Methods: We conducted a prospective single-center cohort study including 58 living-related kidney transplant recipients classified as low- to moderate-risk according to international transplant criteria. All recipients were managed using a structured preventive immunomodulatory protocol incorporating low-dose rabbit anti-thymocyte globulin induction, a single peri-transplant dose of rituximab, standardized three-session peri-transplant plasmapheresis, standard triple maintenance immunosuppression, and structured infection prophylaxis. Patients were followed for 18 months with systematic surveillance for proteinuria, hematuria, and graft dysfunction.

Results: Recipient age ranged from 14 to 58 years; 30% were female. At 18 months, patient survival was 100% and graft survival was preserved in the entire cohort. Acute cellular rejection occurred in 2 recipients (3.4%), both steroid responsive; no antibody-mediated rejection events were observed. Two recipients (3.4%) developed cytomegalovirus colitis and recovered fully; one recipient developed bacterial urinary tract infection; no BK polyomavirus nephropathy occurred. During follow-up, 4 recipients (6.9%) developed new-onset proteinuria and one also developed microscopic hematuria; all four underwent indication kidney biopsy. Biopsy-proven recurrent glomerular disease was identified in 3 recipients (5.2%): two recurrent focal segmental glomerulosclerosis and one recurrent immunoglobulin A nephropathy. The remaining biopsy demonstrated transplant glomerulopathy attributed to calcineurin inhibitor toxicity. Nephrotic-range focal segmental glomerulosclerosis recurrence and immunoglobulin A nephropathy recurrence were associated with progressive creatinine elevation but retained functioning grafts at study completion.

Conclusion: In selected low- to moderate-risk living-related kidney transplant recipients with uncertain primary renal disease, a preventive immunomodulatory strategy was associated with low acute rejection rates and limited early recurrence events. Multicenter validation and longer follow-up are warranted.

Keywords: kidney transplantation; living-related donor; induction therapy; anti-thymocyte globulin; rituximab; plasmapheresis; recurrence; focal segmental glomerulosclerosis; immunoglobulin A nephropathy; transplant glomerulopathy

Introduction

Kidney transplantation is the preferred renal replacement therapy for most patients with end-stage kidney disease because it improves survival and quality of life compared with long-term dialysis.[1] Despite major advances in surgical technique and immunosuppressive therapy, long-term allograft survival remains constrained by acute rejection, chronic alloimmune injury, calcineurin inhibitor nephrotoxicity, infections, and recurrence of the original kidney disease.[2,3]

Contemporary pretransplant risk stratification is largely anchored to alloimmune metrics: human leukocyte antigen mismatch, donor-specific antibody status, panel reactive antibody levels, and complement-dependent cytotoxic crossmatch.[2] These tools guide induction choices ranging from interleukin-2 receptor antagonists to lymphocyte-depleting agents (eg, rabbit anti-thymocyte globulin).[2] Yet, for a clinically important subset of recipients—particularly young or nondiabetic patients with uncertain or incompletely characterized native kidney disease—standard alloimmune risk estimates may not capture recurrence driven by circulating permeability factors, complement dysregulation, or non–human leukocyte antigen immune pathways.[4,5]

Uncertain primary renal disease is common in transplant programs because native kidney biopsy may be unavailable or nondiagnostic, patients may present late with advanced scarring, or prior medical records are incomplete.[2] When the primary diagnosis is unclear, clinicians face a dilemma: use conventional low-risk induction and accept the possibility of early recurrence, or apply more intensive preventive strategies with attendant infection and toxicity risks.[3]

Recurrent focal segmental glomerulosclerosis can be early and aggressive; consensus statements emphasize that recurrence risk is highest in idiopathic disease and in those with rapid progression or previous graft recurrence.[4] Recurrent immunoglobulin A nephropathy is frequent with longer follow-up and may present with hematuria and proteinuria; biopsy confirmation is essential to distinguish recurrence from other causes of allograft injury and to distinguish recurrent disease from de novo immunoglobulin A deposits.[5,6]

Preventive or preemptive strategies for recurrence have included peri-transplant plasmapheresis and B-cell modulation, reflecting hypotheses about circulating factors and humoral pathways in selected diseases.[4,7] However, intensifying immunosuppression increases risks of viral and opportunistic infections; implementation therefore requires robust prophylaxis and surveillance frameworks.[8,9]

In this context, the Arab Renal Care Group developed a structured preventive immunomodulatory protocol for recipients categorized as low to moderate alloimmune risk but considered at potential risk for glomerular recurrence because of uncertain primary renal disease or suspected immune-mediated etiologies. This study describes 18-month outcomes with emphasis on rejection, infection, and biopsy-defined recurrence events detected via structured surveillance.

Methods

STUDY DESIGN AND SETTING

This prospective single-center cohort enrolled consecutive living-related donor kidney transplant recipients between January 2021 and December 2024. Patients were followed for 18 months post-transplant.

ETHICAL CONSIDERATIONS

The study was conducted in accordance with the principles of the Declaration of Helsinki. Institutional review and/or ethical oversight was obtained per local requirements, and patients provided consent for standard-of-care data collection and follow-up.

PARTICIPANTS

Inclusion criteria were living-related donor transplantation, low- to moderate-risk alloimmune profile, uncertain or suspected immune-mediated native kidney disease, and negative complement-dependent cytotoxic crossmatch. Exclusion criteria

were detectable donor-specific antibodies, ABO incompatibility, prior transplantation, or panel reactive antibody >20%.

RISK STRATIFICATION

Risk stratification followed international transplant guidance and local practice using panel reactive antibody and donor-specific antibody screening, complement-dependent cytotoxic crossmatch, and human leukocyte antigen mismatch.[2] 'Moderate risk' designation also included recipients with suspected immune-mediated glomerular etiologies (eg, suspected focal segmental glomerulosclerosis or immunoglobulin A nephropathy) even when donor-specific antibody testing and crossmatch were negative.

PREVENTIVE IMMUNOMODULATORY PROTOCOL

Induction therapy consisted of rabbit anti-thymocyte globulin with a cumulative dose of 3–4.5 mg/kg (dose-tailored). Reduced-dose strategies have been evaluated in selected populations and may reduce acute rejection while limiting infectious complications.[10,11] B-cell modulation consisted of a single peri-transplant rituximab dose (200 mg). Plasmapheresis consisted of three standardized peri-transplant sessions for all recipients. Maintenance therapy consisted of tacrolimus, mycophenolate mofetil, and a corticosteroid taper.

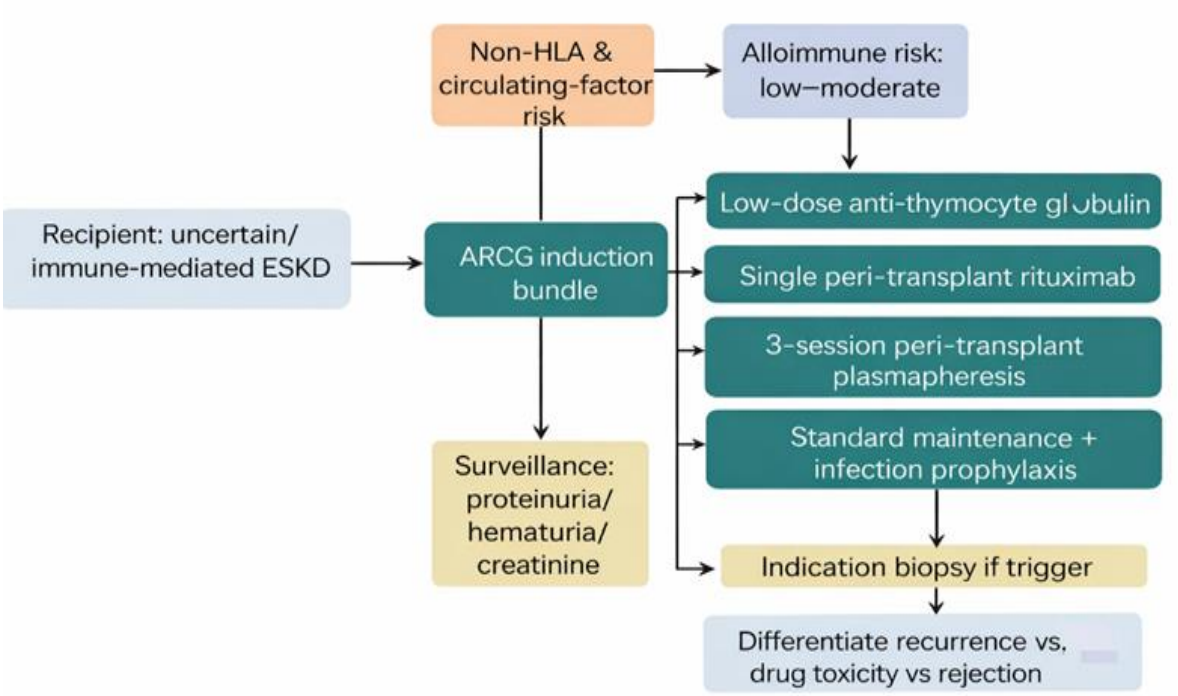

Chart 1 :Kidney transplant protocol flowchart

INFECTION PROPHYLAXIS AND VIRAL SURVEILLANCE

Infection prophylaxis was standardized and aligned with contemporary consensus guidance for cytomegalovirus and BK polyomavirus management in solid organ transplantation.[8,9] Viral surveillance included scheduled monitoring for cytomegalovirus disease and BK polyomavirus DNAemia, with prespecified thresholds prompting diagnostic evaluation and immunosuppression adjustment.

GLOMERULAR DISEASE SURVEILLANCE AND INDICATION BIOPSY

Surveillance included serial serum creatinine, urinalysis, hematuria assessment, and quantitative proteinuria. Indication biopsy was performed for new-onset proteinuria, nephrotic syndrome, persistent microscopic hematuria, or unexplained graft dysfunction. Biopsies were interpreted using contemporary renal allograft pathology standards and clinicopathologic correlation.[3,12] When recurrent glomerular disease was suspected, histopathology

was adjudicated in the differential of rejection, transplant glomerulopathy, and calcineurin inhibitor toxicity.

OUTCOMES AND ANALYSIS

Primary outcomes were acute rejection, patient survival, and graft survival. Secondary outcomes were biopsy-proven recurrence, cytomegalovirus disease, BK polyomavirus nephropathy, and other clinically significant infections. Analyses were descriptive; Kaplan–Meier methods were used for time-to-event visualization.

Results

BASELINE CHARACTERISTICS

Recipients ranged from 14 to 58 years; 30% were female. All donors were living-related. Etiology of kidney failure was categorized as: unknown (63%), nondiagnostic native biopsy (8%), focal segmental glomerulosclerosis (18%), and immunoglobulin A nephropathy (11%). Sixty-five percent met ‘low risk’ alloimmune criteria and 35% were ‘moderate risk’ by study definition.

Table 1. Recipient Baseline Characteristics

Variable	Value
Number of recipients	58
Age range, years	14–58
Female, n (%)	17 (29.3%)
Male, n (%)	41 (70.7%)
Follow-up duration	18 months
Hypertension, n (%)	58 (100.0%)

Table 2. Etiology of End-Stage Kidney Disease

Etiology	n (%)
Unknown (no biopsy)	37 (63.8%)
Nondiagnostic native biopsy	5 (8.6%)
Focal segmental glomerulosclerosis	10 (17.2%)
Immunoglobulin A nephropathy	6 (10.3%)

Table 3. Donor Characteristics

Variable	Value
Living-related donors	58 (100%)
Age range, years	26–52
Male donors, n (%)	41 (70.7%)
Female donors, n (%)	17 (29.3%)

Table 4. Immunologic Risk Stratification

Risk group	Definition	n (%)
Low risk	PRA negative, CDC negative, HLA ≤4 mismatch, no DSA	38 (65.5%)
Moderate risk	HLA 5–6 mismatch and/or suspected immune-mediated glomerulonephritis	20 (34.5%)

CLINICAL OUTCOMES

At 18 months, patient survival was 100% and graft survival was preserved in the entire cohort. Acute cellular rejection occurred in 2 recipients (3.4%) and was biopsy-proven; both cases were steroid responsive. No antibody-mediated rejection events were observed.

INFECTIOUS OUTCOMES

Two recipients (3.4%) developed cytomegalovirus colitis and recovered fully. One recipient developed bacterial urinary tract infection. No BK polyomavirus nephropathy occurred.

Table 5. Clinical and Infectious Outcomes Through 18 Months

Outcome	n (%)
Patient death	0 (0.0%)
Graft loss (return to dialysis or re-transplant)	0 (0.0%)
Acute cellular rejection (biopsy-proven)	2 (3.4%)
Antibody-mediated rejection (biopsy-proven)	0 (0.0%)
Cytomegalovirus colitis	2 (3.4%)
Bacterial urinary tract infection	1 (1.7%)
BK polyomavirus nephropathy	0 (0.0%)
New-onset proteinuria prompting evaluation	4 (6.9%)
Indication allograft biopsy performed	4 (6.9%)
Biopsy-proven recurrent glomerular disease	3 (5.2%)
Transplant glomerulopathy attributed to calcineurin inhibitor toxicity	1 (1.7%)

GLOMERULAR DISEASE SURVEILLANCE AND RECURRENCE

During the follow-up period, 4 recipients (6.9%) developed new-onset proteinuria; one of these patients also presented with microscopic hematuria. All four patients underwent indication allograft biopsy. Biopsy-proven recurrent glomerular disease was identified in 3 recipients (5.2% of the total cohort): two cases of focal segmental glomerulosclerosis and one case of immunoglobulin A nephropathy. The remaining biopsy demonstrated transplant glomerulopathy attributed to calcineurin inhibitor toxicity.

Graft function remained stable in two recipients (one mild focal segmental glomerulosclerosis recurrence and the transplant glomerulopathy case after clinical management). Nephrotic-range focal segmental glomerulosclerosis recurrence and immunoglobulin A nephropathy recurrence were associated with progressive creatinine elevation but retained functioning grafts at the end of follow-up.

Table 6. Indication Allograft Biopsies Triggered by Proteinuria/Hematuria Surveillance (n=4)

Case	Clinical trigger	Biopsy finding	Clinical urinary findings	Renal function course by 18 months
1	Nephrotic syndrome	Recurrent focal segmental glomerulosclerosis	Nephrotic-range proteinuria	Progressive creatinine rise; graft functioning
2	Proteinuria	Recurrent focal segmental glomerulosclerosis	Sub-nephrotic proteinuria	Stable function
3	Proteinuria + microscopic hematuria	Recurrent immunoglobulin A nephropathy	Non-nephrotic proteinuria + microscopic hematuria	Progressive creatinine rise; graft functioning
4	Proteinuria	Transplant glomerulopathy (calcineurin inhibitor toxicity)	Sub-nephrotic proteinuria	Stabilized with management

Table 7. Biopsy-Proven Recurrence Stratified by Native Kidney Diagnosis Category

Native kidney diagnosis category	n in cohort	Biopsy-proven recurrence, n	Recurrence, % within category	Recurrence, % of whole cohort
Focal segmental glomerulosclerosis	10	2	20.0	3.4
Immunoglobulin A nephropathy	6	1	16.7	1.7
Unknown or nondiagnostic	42	0	0.0	0.0

Discussion

This prospective cohort suggests that a structured preventive immunomodulatory strategy in selected living-related kidney transplant recipients with uncertain primary renal disease is feasible and was associated with low acute cellular rejection and preserved patient and graft survival at 18 months.

INDUCTION AND REJECTION

The 3.4% acute cellular rejection rate compares favorably with historical series in similar living-donor settings. Reduced-dose rabbit anti-thymocyte globulin has been evaluated as an alternative to basiliximab in selected low-risk living-donor transplantation cohorts, with comparable rejection and infection outcomes in retrospective analyses.[10] In broader registry-based populations, dose-response relationships for anti-thymocyte globulin induction appear heterogeneous, reinforcing the need for population-specific evaluation and confounding control.[11]

RECURRENCE DETECTION AND INTERPRETATION

Systematic surveillance for proteinuria and hematuria, coupled with timely indication biopsy, enabled biopsy-based attribution of recurrence versus alternative diagnoses. All four recipients with new proteinuria underwent biopsy; three had recurrent glomerular disease and one had transplant glomerulopathy attributed to calcineurin inhibitor toxicity. This underscores that not all post-transplant

proteinuria reflects recurrence and that clinicopathologic correlation remains essential.[3,12]

FOCAL SEGMENTAL GLOMERULOSCLEROSIS RECURRENCE

Consensus statements emphasize that recurrent focal segmental glomerulosclerosis is often early and clinically severe, and that definitive predictors remain limited outside of prior graft recurrence and clinical phenotyping.[4] Evidence for prophylactic plasmapheresis and rituximab is heterogeneous. A contemporary systematic review in Clinical Kidney Journal observed modest recurrence reduction with preventive strategies and suggested that rituximab does not clearly add benefit beyond plasma exchange in initial treatment.[7] A separate single-center cohort reported lower early clinical recurrence with peri-transplant plasma exchange plus rituximab compared with historical controls, though limitations include retrospective design and protocol-to-control era effects.[13] In the present cohort, one recurrent focal segmental glomerulosclerosis case presented with nephrotic-range proteinuria and progressive creatinine rise, while a second recurrence was sub-nephrotic with stable function, illustrating the spectrum of recurrence severity.

IMMUNOGLOBULIN A NEPHROPATHY RECURRENCE AND EMERGING THERAPIES

Immunoglobulin A nephropathy recurrence is common over long-term follow-up and is influenced by surveillance intensity and biopsy thresholds. In a 2024 living-donor series, recurrence occurred in approximately 16% of recipients with immunoglobulin A nephropathy, with variable time to recurrence and heterogeneity in management.[6] A 2023 systematic review and meta-analysis identified multiple proposed recurrence risk factors and confirmed association between recurrence and increased risk of graft loss.[5] Emerging therapies targeting mucosal immunity and the BAFF/APRIL axis are beginning to appear in transplant recurrence reports, including targeted-release budesonide and telitacicept for recurrent immunoglobulin A nephropathy.[14,15] Early transplant-case experience with complement factor B inhibition (iptacopan) has also been reported, building on the phase 3 trial evidence for proteinuria reduction in native immunoglobulin A nephropathy.[16,17]

INFECTIOUS OUTCOMES AND SAFETY

Infectious events were limited (two cases of cytomegalovirus colitis, no BK polyomavirus nephropathy). Because intensified immunomodulation can predispose to viral complications, the observed safety profile should be interpreted alongside standardized prophylaxis and surveillance.[8,9] Contemporary consensus guidance supports proactive BK polyomavirus DNAemia screening schedules and stepwise immunosuppression reduction, and similar consensus documents guide cytomegalovirus prevention and management.[8,9]

STRENGTHS AND LIMITATIONS

Strengths include prospective follow-up, structured surveillance triggering biopsy evaluation for new proteinuria or hematuria, and biopsy-based recurrence adjudication. Limitations include single-center design, modest sample size, and 18-month follow-up, which is short for immunoglobulin A nephropathy recurrence assessment. Because most recipients had uncertain native diagnoses, recurrence rates stratified by native category should be interpreted cautiously.

Conclusion

A preventive immunomodulatory protocol combining reduced-dose rabbit anti-thymocyte globulin induction, peri-transplant rituximab, and standardized plasmapheresis was associated with low rejection and limited early biopsy-proven recurrence events, with preserved patient and graft survival at 18 months. Larger multicenter comparative studies are needed to clarify effectiveness, define optimal candidate selection, and better characterize long-term recurrence prevention.

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