Global Kidney Trial Watch (ISN TrialWatch)
Oct-Nov-Dec 2025

The ISN-ACT (Advancing Clinical Trials) team presents this bi-monthly round up of randomized trials in nephrology. Trials are selected not just for impact, but also to showcase the diversity of research produced by the global nephrology community. Each trial is reviewed in context and has a risk of bias assessment. We hope to drive improvement in trial quality and promote greater engagement in trial activity.

Key to risk of bias assessment

- (R) Random sequence generation
- (A) Allocation concealment
- (BP) Blinding of participants/personnel
- (BO) Blinding of outcome assessment
- (CD) Complete outcome data
- (CR) Complete outcome reporting
- (B) No other sources of bias

High risk
Uncertain risk / not stated
Low risk

Do you agree with our trial of the month? Tell us what you think!
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ISN Academy: Transplant

IVIG Modulates Fibrosis and Stabilizes Chronic Active AMR Progression

A randomized controlled trial of intravenous immunoglobulin vs standard of care for the treatment of chronic active antibody-mediated rejection in kidney transplant recipients

Mulley et al., Kidney Int. 2025 Sep;108(3):470-480.

R A BP BO CD CR B

Reviewed by Anastasiia Zykova

Summary: Chronic active antibody-mediated rejection (AMR) is the primary cause of kidney allograft loss beyond 5 years and currently has no evidence-based long-term therapy. This prospective multicenter RCT evaluated whether IVIG could modify disease progression in adults with biopsy-proven chronic active AMR diagnosed more than 6 months after transplantation. Participants (n=30) were randomized to receive IVIG (1 g/kg monthly for three consecutive months, followed by further infusions after verification of microvascular inflammation by graft biopsy) or no IVIG, while receiving standardized immunosuppression and pulse steroids. The primary endpoint was the change in the Chronic Allograft Damage Index (CADI). IVIG stabilized CADI scores over 12 months, while the no-IVIG group showed a steady increase driven by growing glomerulosclerosis, interstitial fibrosis, and tubular atrophy. eGFR decline was also slower with IVIG (–0.4 vs –1.1 ml/min/1.73 m² per month). IVIG, however, did not reduce donor-specific antibodies or microvascular inflammation. Gene expression profiling revealed significant downregulation of 59 genes in IVIG-treated grafts, predominantly in pathways related to B cells, NK cells, T cells, inflammation, and fibrosis. These changes persisted after IVIG cessation. Allograft failure was lower, whereas mortality was significantly higher in the no-IVIG group, although the trial was underpowered for survival outcomes. IVIG was well tolerated, with infrequent infusion-related events.

Comment: This is the first adequately designed RCT to show a clinically meaningful effect of IVIG in chronic active AMR. While previous trials of proteasome inhibitors, complement inhibitors, IL-6 blockade, and IVIG/anti-CD20 combinations had failed to show benefit, this study employed higher cumulative IVIG dosing and repeated protocol biopsies, providing a clearer view of disease dynamics. A key insight is that IVIG does not act by reducing DSAs or microvascular inflammation—classical markers of AMR—but instead by modifying graft inflammatory and fibrotic pathways. The stabilization of chronic injury scores and concordant gene transcript changes suggests a shift in the local immune environment rather than upstream antibody effects. Although the study was modest in size, its consistency across histology, function, and transcriptomics strengthens the conclusions. Given the lack of alternatives, IVIG seems

appropriate as supportive therapy for chronic active AMR and should likely serve as the standard-of-care comparator in future trials examining agents that target complement, plasma cells, or NK-cell–mediated injury.

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*ISN Academy: **Transplant***

Intra-arterial application of C1 esterase inhibitor may enhance kidney allograft function at six months in patients with a high risk of delayed graft function

Back-table intra-arterial administration of C1 esterase inhibitor to deceased donor kidney allografts improves posttransplant allograft function: Results of a randomized double-blind placebo-controlled clinical trial

Huang et al. Am J Transplant. 2025 Sep;25(9):1926-1939.

Reviewed by Nikolina Basic-Jukic

Summary: In this randomized, double-blind, placebo-controlled pilot trial, 40 adult recipients of deceased-donor kidney transplants, considered high risk for developing delayed graft function (DGF), were randomly assigned to receive either intraoperative C1 esterase inhibitor (C1INH) at a dose of 500 IU, administered via the transplant renal artery 1- 2 hours before implantation, or a placebo. Primary outcomes included: 1) DGF, defined as the proportion of patients requiring at least one dialysis session within the first 30 days after transplant (excluding those dialyzed solely for hyperkalemia); 2) the number of dialysis sessions per patient within the first 30 days post-transplant; 3) estimated glomerular filtration rate (eGFR); 4) graft survival; and 5) patient survival at 6 months. The primary safety endpoint was the overall incidence of adverse and serious adverse events (AEs and SAEs) up to 6 months post-procedure. At six months, the eGFR was significantly higher in the C1INH group (median 55 mL/min/1.73 m², IQR 42-63) compared to placebo (median 39 mL/min/1.73 m², IQR 34-50; P = .02). There was no significant difference in the proportion of patients requiring dialysis within 30 days post-transplant (C1INH: 50% vs. placebo: 45%; P = .10). Immunofluorescence showed C4d presence in control grafts' blood vessels and glomeruli, but levels were significantly lower in C1INH-treated grafts. Quantitative analysis confirmed higher C1INH levels in treated allografts. No differences between groups were observed in the types of adverse events.

Comment: C1 esterase inhibitor (C1INH) is an endogenous serine protease inhibitor that regulates vascular permeability, inflammation, coagulation, and complement activation. The present study suggests that C1INH may enhance kidney allograft function independently of DGF, likely by inhibiting local complement activation within the graft. Limitations include its single-center design and small sample size, and it was not designed to detect differences in adverse events. The definition of DGF remains debated, though most recent studies define it as the need for dialysis within the first 7 days post-transplant. Future research with larger cohorts and longer follow-up is needed to determine if six-month improvements in graft function translate into long-term benefits.

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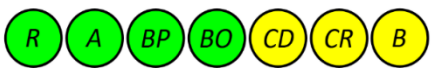
*ISN Academy: **Dialysis***

DIALIZE-Outcomes: Potassium Controlled, Cardiovascular Risk Unchanged

The randomized DIALIZE-Outcomes trial evaluated sodium zirconium cyclosilicate in hemodialysis

Fishbane et al. Kidney Int. 2025 Oct;108(4):686-694.



Reviewed by Anastasiia Zykova

Summary: Sodium zirconium cyclosilicate (SZC) is an effective potassium binder that normalizes serum K^+ in non-dialysis CKD patients and in earlier DIALIZE studies of hemodialysis patients. The phase 3, event-driven, DIALIZE-Outcomes trial evaluated whether SZC reduces major arrhythmia-related cardiovascular events (sudden cardiac death, stroke, arrhythmia-related hospitalization/intervention/emergency department visit) in hemodialysis patients with recurrent pre-dialysis hyperkalemia (≥ 5,5 mmol/l). Over 2600 randomized participants received SZC or placebo on non-dialysis days, starting at 5 g orally and titrating to individualized doses. The mean age was 56.1 years (SD 13.4). Sixty-two percent were male, mainly White (50.6%) or Asian (29.0%). Baseline pre-dialysis serum potassium levels were similar between groups, averaging 6.0 mmol/l (SD 0.7). Dialysis parameters, including adequacy and interdialytic weight gain, were comparable. Most participants had hypertension; about one-third each had dyslipidemia and type 2 diabetes. The study was terminated by the sponsor early due to low event rates, only one-third of planned events had occurred, and high study medication discontinuation (particularly in the placebo arm). Mean durations of exposure were 12.4 and 11.3 months for the SZC and placebo groups, respectively. SZC did not reduce the primary composite cardiovascular outcome (HR 0.98; 95% CI 0.76 - 1.26). Secondary cardiovascular endpoints similarly showed no differences. However, SZC significantly improved biochemical control: more patients maintained normokalemia,

fewer developed severe hyperkalemia, and fewer required rescue therapy. Safety was comparable to placebo, with similar rates of adverse and serious adverse events.

Comment: Patients with kidney failure often develop persistent hyperkalemia, even with thrice-weekly hemodialysis, and rapid potassium shifts during dialysis increase the risk of arrhythmias and sudden cardiac death. The trial confirms that SZC effectively manages serum potassium in hemodialysis patients but does not demonstrate a cardiovascular benefit, likely due to limited statistical power, low event rates, modest baseline K^+ levels, and the complex, nonlinear relationship between potassium and arrhythmias. Early termination due to low event rate and high discontinuation rates further hindered interpretation. The study population was relatively young compared to the typical in-center dialysis population and had a short follow-up duration; therefore, the low event rate was not surprising. Thus, a more extended follow-up period could have yielded more events. Although SZC enhances biochemical stability, this study does not support its use to reduce the risk of arrhythmia-related cardiovascular events specifically.

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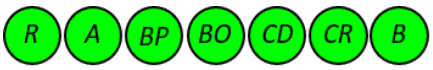
*ISN Academy: **Glomerular Diseases***

Felzartamab in IgA Nephropathy: Proof of Concept for Plasma Cell–Directed Therapy

Randomized, double-blind, placebo-controlled phase 2a study assessing the efficacy and safety of felzartamab for IgA nephropathy

Floege et al., Kidney International (2025) 108, 695–706.



Reviewed by Anastasiia Zykova

Summary: This randomized, double-blind, placebo-controlled, phase 2a study evaluates felzartamab, an investigational anti-CD38 monoclonal antibody, in patients with biopsy-proven IgA nephropathy (IgAN) and persistent proteinuria despite RAS blockade. The study was conducted in two parts. In part 1, 48 patients were randomized to placebo or to felzartamab and received 2-, 5-, or 9-dose regimens over 6 months, followed by 24 months of off-treatment follow-up. An additional open-label cohort of six Japanese patients received the 9-dose regimen in part 2. The primary endpoint was the change in 24-hour urine protein-to-creatinine ratio (UPCR) at 9 months. Felzartamab produced dose-dependent reductions in proteinuria, with the largest and most durable effect observed in the 9-dose group. Proteinuria reduction was evident by month 3 and was sustained through 24 months, particularly in the highest-dose arm. The decline in estimated glomerular filtration rate (eGFR) was consistently smaller in felzartamab-treated patients than in placebo-treated patients. Pharmacodynamic analyses showed marked reductions in total IgA and Gd-IgA1 during treatment, with slower recovery after treatment cessation at higher doses. IgG and IgM levels recovered more rapidly. Felzartamab was generally well tolerated; most adverse events were mild to moderate, with infusion-related reactions the most common treatment-related events.

Comment: Felzartamab targets CD38-expressing plasmablasts and plasma cells to reduce production of galactose-deficient IgA1 (Gd-IgA1) and pathogenic autoantibodies central to the “four-hit” model of IgAN. The IGNAZ study provides proof of concept that targeting CD38-positive plasma cells can influence upstream pathogenic mechanisms in IgAN. Unlike rituximab, which did not improve outcomes, felzartamab directly targets antibody-secreting cells responsible for sustained Gd-IgA1 production. The simultaneous reductions in IgA biomarkers, proteinuria, and eGFR decline support the approach's biological plausibility. A key strength is the extended follow-up, which demonstrates a durable decrease in proteinuria for up to 18 months after therapy discontinuation, particularly with the 9-dose regimen. This contrasts with glucocorticoids, where relapse is common after withdrawal. The trend toward slower eGFR decline suggests potential disease modification. Limitations include a small sample size, baseline imbalances, wide confidence intervals, and possible confounding from glucocorticoid use for pre-medication and rescue therapy. The higher incidence of infusion reactions underscores the need for safety monitoring. Overall, felzartamab demonstrates promising efficacy and a mechanism of action in IgAN. Larger phase 3 trials are needed to confirm benefits, optimize dosing, and assess long-term safety.

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*ISN Academy: **Chronic Kidney Disease***

SGLT2 inhibitors for improving erectile dysfunction in non-diabetic CKD patients: a randomized pilot study

Sodium glucose co-transporter 2 inhibitors (SGLT2Is) effect on erectile dysfunction (ED) in patients with chronic kidney disease (CKD)

Shaker, AM et al., Clin Exp Nephrol. 2025 Oct;29(10):1394-1399.

Reviewed by Chiara Ruotolo

Summary: This randomized study investigated whether sodium–glucose co-transporter-2 inhibitors (SGLT2i) improve erectile dysfunction (ED) in adult male patients with chronic kidney disease (CKD). Thirty-four non-diabetic CKD patients aged 18–65 years (eGFR ≥20 mL/min/1.73 m²) were enrolled after excluding alternative causes of ED through clinical evaluation, hormonal testing, and penile Doppler imaging. Participants were randomly assigned to receive empagliflozin 10 mg (n=17) or dapagliflozin 10 mg (n=17) once daily for 3 months. Baseline demographic and clinical characteristics were broadly comparable, aside from differences in some metabolic parameters. Erectile function was assessed using the IIEF-5 questionnaire before and after treatment. After 3 months, both SGLT2 inhibitors produced significant improvements in erectile function ($P < 0.001$), alongside better renal parameters including higher eGFR and lower serum creatinine, triglycerides, and LDL cholesterol. No meaningful differences were detected between empagliflozin and dapagliflozin in post-treatment outcomes.

Comment: Erectile dysfunction is a common and frequently under-recognized complication of CKD, often linked to endothelial dysfunction, inflammation and the vascular effects of uremia. The potential for SGLT2 inhibitors to improve ED—beyond their established renal and cardiovascular benefits—represents a clinically meaningful avenue, particularly given their favorable endothelial and anti-inflammatory actions proposed in experimental studies. This small, randomized study offers preliminary support for a possible role of SGLT2 inhibitors in improving ED among non-diabetic CKD patients. However, several limitations warrant caution. The small sample size and short follow-up reduce statistical power and limit assessment of long-term effects. The absence of a placebo or standard-of-care comparator makes it difficult to attribute improvements specifically to SGLT2 inhibition. Additionally, baseline imbalances raise potential for residual confounding. Despite these constraints, the findings suggest a promising therapeutic direction. Larger, controlled studies—ideally comparing SGLT2 inhibitors with PDE5 inhibitors or combination approaches—are needed to clarify their role in the management of ED in CKD.

Edited by Neeru Agarwal, Megan Borkum, Michele Provenzano, Mohammed Elrgal and Anastasiia Zykova