ISN TrialWatch

April-May-June 2026

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: CKD

A new approach to Diabetic Kidney Disease: Autologous Cell Therapy

A Randomized Clinical Trial of Kidney Autologous Cell Therapy in Diabetic Kidney Disease

Cizman et al., 2026 DOI: 10.2215/CJN.0000000969

R A BP BO CD CR B

Reviewed by Ahad Qayyum

Summary: This phase 2, multi-center, open-label randomized clinical trial (REGEN-007, NCT05018416) assessed whether autologous cell therapy (rilparencel) can slow the progression of diabetic kidney disease. Fifty-three participants from 5 sites were randomized 1:1 into two cohorts. All participants were diabetics (type 1 or type 2) with an estimated glomerular filtration rate of 20–50 ml/min/1.73 m2 and a urine albumin to creatinine ratio of 30–5000 mg/g. Rilparencel was derived from each participant via image-guided percutaneous kidney biopsy and subsequent processing with enzymatic digestion, ex vivo cell culture and centrifugation techniques to select epithelial kidney cells. Cohort 1 received two percutaneous rilparencel injections into the kidney cortex under CT guidance, administered three months apart, one in each kidney. Cohort 2 received a single injection initially, with a second injection administered only in the event of a sustained decline in eGFR or an increase in urinary albumin creatinine ratio. Participants were followed for up to 18 months after their last injection. The primary efficacy end point was a change in the eGFR slope between the historical preinjection period and the period after the last injection. The primary safety end point was the percentage of participants with procedure or rilparencel-related treatment emergent adverse events (TEAEs). In Cohort 1, the annual eGFR slope improved from -5.84 to -1.27ml/min/1.73m2/year (difference 4.57; 95% CI, 1.95 to 7.18). Similarly, in Cohort 2, the annual eGFR slope changed from -3.40 to -1.71ml/min/1.73m2/year (difference 1.70; 95% CI, -0.24 to 3.63). The more pronounced effect in Cohort 1 was attributed to greater rilparencel exposure, as 96% of participants received two injections (median interval, 4 months) compared with 60% in Cohort 2 (median interval, 11 months). Of 87 injections, procedure-related TEAEs occurred in 16 participants and rilparencel-related TEAEs occurred in six participants. There were no product-related serious adverse events and no procedure-related or product-related deaths. A sham-controlled phase 3 trial (NCT05099770) is ongoing.

Comment: Rilparencel represents a genuinely novel concept in CKD therapy. The four established pillars of diabetic kidney disease therapy (RAS blockade, SGLT2-inhibitors, GLP-1 receptor agonists and nonsteroidal MRAs) primarily act

by modifying the millieu in which nephrons operate, thereby decelerating decline. Rilparencel seeks to augment functional tissue by using a patient's own expanded kidney cells. This shift from 'protecting' residual kidney function to 'regenerating' it is a unique and novel contribution this trial makes to existing treatment approaches. Because the product is autologous, it also avoids the immunogenicity that has limited earlier allogenic and stem-cell approaches. This is particularly important because, despite optimized current therapy, many patients continue to progress to kidney failure, and there remain few new mechanistic options for them.

However, the trial design has important limitations. The efficacy assessment relies on a within-patient comparison against a historical eGFR slope rather than a concurrent control group. The cohorts are also not directly comparable, and the small, predominantly White male population limits generalizability. Although the safety profile is reassuring, the main risks are procedural. The ongoing sham-controlled phase 3 trial (NCT05099770) is therefore the necessary next step. Future work should also clarify the underlying mechanism, particularly the lack of effect on albuminuria, determine the optimal dosing, and identify the patients most likely to benefit.

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*ISN Academy: **Transplant***

Dapagliflozin in Kidney Transplant Recipients: familiar effects, undefined mechanism

Efficacy, Mechanisms, and Safety of Sodium-Glucose Cotransporter-2 Inhibitors in Kidney Transplant Recipients: A Randomized, Double-Blind, Placebo-Controlled Trial

Sridhar et al., 2026 DOI:10.2215/CJN.0000000951

R A BP BO CD CR B

Reviewed by Nikolina Basic-Jukic

Summary: This single-center, double-blind, placebo-controlled, parallel-group trial included 52 kidney transplant recipients, with and without type 2 diabetes, who underwent physiological assessments at baseline and 1 and 12 weeks after receiving dapagliflozin 10 mg or placebo under standardized euglycemic conditions. The primary objective was to investigate the blood pressure–lowering effects of dapagliflozin, while secondary endpoints focused on renal function, sodium handling, body composition, hemodynamic parameters, arterial stiffness, autonomic function, neurohormonal responses, and treatment safety.

A total of 51 participants completed the study. The cohort mean age was 53±13 years, 62% had hypertension, 57% had type 2 diabetes, 50% received renin-angiotensin-aldosterone system inhibitors, and 88% were on triple immunosuppression (tacrolimus, mycophenolate, and prednisone). The mean eGFR was 68.2±24.4 ml/min per 1.73 m^2. Dapagliflozin did not lower systolic BP at 1 or 12 weeks compared with placebo, although it reduced mean arterial pressure after 1 week (3.9 mm Hg; 95% CI, -7.5 to -0.2). Use of dapagliflozin was associated with significant, placebo-adjusted reductions in iohexol-measured GFR from baseline to 1 week (4.2 ml/min per 1.73 m^2; 95% CI, -7.14 to -1.24 ml/min per 1.73 m^2) and 12 weeks (-3.49 ml/min per 1.73 m^2; 95% CI, -6.33 to -0.64). It significantly increased glucosuria and urine volume without altering proximal sodium handling, without evidence of sympathetic activation, and without any change in albuminuria. Acute non-significant decreases in arterial stiffness (carotid augmentation index, -3.5%; 95% CI, -6.0 to -1.1) were observed in the dapagliflozin group after 12 weeks. No episodes of urinary tract or genitourinary infections, ketoacidosis, or significant AKI were reported during the study.

Comment: This study adds to the growing body of evidence supporting the use of SGLT2 inhibitors in kidney transplant recipients by providing important insights into their physiological effects. While dapagliflozin produced several expected responses, including increased glucosuria and an early decline in GFR, some of the findings differed from those reported in non-transplant populations. These differences may reflect the unique characteristics of transplant recipients, particularly the influence of immunosuppressive therapy and the altered renal physiology of the allograft after transplantation.

One of the most interesting observations was the apparent disconnect between glucose excretion and sodium handling, with robust glucosuria but no significant increase in proximal natriuresis. This raises questions about whether the mechanisms underlying the cardiorenal benefits of SGLT2 inhibitors operate the same way in transplant recipients as in the general CKD population. Further studies are therefore needed to better understand the early natriuretic effects of these agents, their interaction with calcineurin inhibitors, and the role of osmotic diuresis in shaping their overall physiological impact.

Equally important is the reassuring safety profile: the absence of genitourinary infections, ketoacidosis, or significant AKI, and the fact that no participant experienced a GFR decline greater than 30% directly address longstanding concerns about SGLT2 inhibitor use in this population. Although the study was not designed to assess long-term clinical outcomes, its findings are important for safety and provide a rationale for future research. Larger studies with longer follow-up are necessary to determine whether the observed physiological changes translate into benefits for graft function, cardiovascular health, and long-term patient survival. Overall, this work represents an important step toward defining the role of SGLT2 inhibitors in kidney transplantation.

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*ISN Academy: **Glomerular Diseases***

INTENT to spare: Mycophenolate Mofetil in childhood steroid-sensitive nephrotic syndrome

Mycophenolate mofetil versus prednisone for the initial treatment of idiopathic steroid sensitive nephrotic syndrome in children in Germany (INTENT): a multicenter, open-label, randomized, controlled, parallel-group, non-inferiority, phase 3 trial

Benz et al., 2026 DOI: 10.1016/S2352-4642(25)00373-6

Reviewed by Rupesh Raina

Summary: This multicenter, open-label, parallel-group, non-inferiority phase 3 trial (INTENT) evaluated whether mycophenolate mofetil (MMF) could be used as an initial steroid-sparing strategy in children with a first episode of idiopathic steroid-sensitive nephrotic syndrome. Children aged 1–10 years who achieved remission after initial prednisone/prednisolone induction were randomized 1:1 to receive either MMF (1200mg/m2/day, in two divided doses for 12 weeks) or a standard 12-week prednisone regimen. The trial enrolled 272 children across 37 centers in Germany and assessed whether MMF was non-inferior to prednisone in preventing treated relapse, using a pre-specified non-inferiority margin of 15%.

The primary efficacy outcome was treated relapse within 24 months after completion of initial therapy. MMF was non-inferior to prednisone for this outcome, with treated relapse occurring in 79.1% of children in the MMF group versus 74.8% in the prednisone group (difference 4.3%, 90% CI -4.2 to 12.7; p=0.019). The frequency of frequently relapsing disease and time to first relapse did not differ between groups. Importantly, MMF was associated with substantially lower glucocorticoid exposure and fewer steroid-related adverse effects, including lower rates of hypertension, lower BMI, z-score increase, and fewer behavioral or psychological abnormalities. The trade-off was a higher infection rate in the MMF group (69.9% vs 55.6%).

Comment: INTENT addresses a long-neglected question: whether the steroid burden of initial nephrotic syndrome treatment can be reduced without compromising efficacy. It is the first randomized trial to test a steroid-sparing agent at the time of the first presentation rather than in relapsing disease, making it a meaningful contribution. The central finding is reassuring: mycophenolate mofetil was non-inferior to standard prednisone for preventing treated relapse after a first episode of steroid-sensitive nephrotic syndrome, while substantially reducing glucocorticoid exposure and the associated toxicity of hypertension, weight gain, cushingoid change, and psychological disturbance. For children facing years of relapsing disease, this toxicity reduction is clinically meaningful. However, several caveats apply. The open-label design is a key limitation, particularly for the subjectively assessed toxicity endpoints. The wide 15% non-inferiority margin combined with the early stop for futility leaves the efficacy claim somewhat fragile. The excess infection in the MMF group is also important to consider as a trade-off. Overall, these findings support MMF as a promising initial steroid-sparing option, most compelling for children with pronounced steroid toxicity. However, longer-term safety, cost-effectiveness, and generalizability beyond this single-center German study are required before this approach is adopted as a new standard of care.

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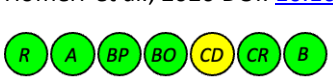
*ISN Academy: **CKD***

IL-33 inhibition in Diabetic Kidney Disease: Target hit, but disease untouched

Inhibition of IL-33 in Diabetic Kidney Disease: A randomised, placebo-controlled phase 2b trial



Reviewed by Michele Provenzano

Summary: The FRONTIER-1 trial was a phase 2b, multicenter, double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of tozorakimab, an IL-33–neutralizing monoclonal antibody, in adults with type 2 diabetes and chronic kidney disease (CKD). A total of 558 participants with an eGFR of 25–75 ml/min/1.73 m² and urinary albumin-to-creatinine ratio (UACR) of 100–3000 mg/g, receiving maximally tolerated renin–angiotensin system blockade, were randomized to receive tozorakimab 30 mg, 60 mg, 120 mg, or 300 mg, or placebo every 28 days for 24 weeks. All participants received dapagliflozin 10 mg daily during days 85–168. At baseline, participants had a mean age of 67 years, mean eGFR of 48 ml/min/1.73 m², and geometric mean UACR of 460 mg/g with 62% having UACR >300 mg/g.

For the primary end point, which was UACR change from baseline to day 169 (per-protocol population), there was no statistically significant difference observed between placebo (-22 %) and any tozorakimab dose group (-23% to -25%), with no dose-response. Similarly, there were no significant differences in the proportion of patients achieving >30%, >40%, or >50% UACR reduction, nor in UACR change before or after dapagliflozin introduction. Tozorakimab was well tolerated, with no substantial difference in treatment-emergent adverse events or serious adverse events compared with placebo; treatment-emergent antidrug antibodies developed in 8–13% of tozorakimab participants versus 1% on placebo.

Exploratory analyses confirmed effective inhibition of IL-33 signaling, with > 95% suppression of the circulating IL-33/sST2 complex across all doses. Of the inflammatory and fibrotic biomarkers assessed, only urinary CCL2 and eosinophil counts showed placebo-adjusted differences. Urinary CCL2 decreased by 29% with the 300 mg dose (90% CI, 14–42%), while eosinophil counts declined by >19% across all doses. No significant differences were observed in cystatin C, eGFR, HbA1c, hemoglobin, or body weight. Overall, although tozorakimab effectively inhibited its intended biological target and favorably modified selected inflammatory biomarkers, it did not reduce albuminuria beyond contemporary standard-of-care therapy in patients with diabetic kidney disease.

Comment: FRONTIER-1 offers important insights into inflammation-targeted therapy in diabetic kidney disease. IL-33 has emerged as a promising therapeutic target after transcriptomic studies showed glomerular upregulation of the cytokine and preclinical work demonstrated that blocking its receptor reduced glomerular damage and albuminuria. By testing tozorakimab, an IL-33–neutralizing monoclonal antibody, this is one of the first large, randomized trials investigating whether selectively inhibiting a specific inflammatory pathway improves kidney outcomes on top of standard-of-care therapy.

Although the trial showed no additional reduction in albuminuria compared with placebo, several findings are noteworthy. Tozorakimab did exactly what it was designed to do – it achieved more than 95% suppression of the circulating IL-33/sST2 complex across all doses, with reduced eosinophil and, at the highest dose, significantly lowered urinary CCL2, confirming target engagement and anti-inflammatory activity. However, this did not translate into improved albuminuria. This is not a failure of dosing or delivery but of the hypothesis, which is what makes the result valuable. Either UACR failed to capture a gradual benefit within a short phase 2 window, or IL-33 and urinary CCL2 are markers of disease progression rather than modifiable therapeutic targets.

A post hoc exploratory analysis suggested a gradual reduction in UACR among participants with a high baseline neutrophil counts (>5.6 × 10^3/µL), who were already receiving SGLT2 inhibitors. This observation raises the possibility that IL-33 inhibition may be more effective in selected pro-inflammatory phenotypes. However, the small, exploratory post hoc nature of the analysis warrants cautious interpretation. Reassuringly, despite profound IL-33 blockade, tozorakimab was well tolerated, with serious adverse events, discontinuations, infections, and deaths comparable to placebo.

Key limitations include the short 24-week duration, reliance on albuminuria as a surrogate, and the mid-trial introduction of dapagliflozin, which lowered placebo-arm UACR and plausibly obscured any drug effect. Despite these limitations, FRONTIER-1 has important strengths, including its double-blind placebo-controlled design, large sample

size, broad dose exploration, and extensive biomarker characterization. Ultimately, FRONTIER-1 underscores the challenges of translating promising anti-inflammatory targets into clinical benefit, and points towards biomarker-defined precision strategies.

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