ISN TrialWatch

Jan-Feb-March 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: Glomerular Disease

TRPC6 Inhibition in FSGS: From Pathogenesis to Precision Treatment

TRPC6 inhibition for the treatment of focal segmental glomerulosclerosis: a randomized, placebo-controlled, phase 2 trial of BI 764198

Trachtman H et al. Lancet. 2026 Feb 7;407(10528):587-598.

R A BP BO CD CR B

Reviewed by Anastasiia Zykova

Summary This phase 2 randomized, double-blind, placebo-controlled trial assessed the efficacy and safety of BI 764198, a selective oral inhibitor of the TRPC6 channel, in adults with biopsy-confirmed primary or TRPC6-related genetic focal segmental glomerulosclerosis (FSGS). Increased TRPC6 activity raises intracellular calcium levels in podocytes, disrupting the cytoskeleton and leading to podocyte loss, proteinuria, and glomerulosclerosis. A total of 62 patients received BI 764198 (20 mg, 40 mg, or 80 mg) or placebo over 12 weeks. Baseline characteristics varied: mean eGFR was 45.5 mL/min/1.73 m² (placebo), 72 (20 mg), 66 (40 mg), and 46 (80 mg). Similarly, baseline 24-hour UPCR was 3.7 g/g (placebo), 4.0 g/g (20 mg), 3.1 g/g (40 mg), and 1.9 g/g (80 mg). The primary endpoint—a ≥25% reduction in urine protein–creatinine ratio (UPCR)—was achieved in 35% of treated patients, compared to 7% in the placebo group. The corresponding odds ratios (ORs) versus placebo were 10.0 (95% CI, 1.6–118.1), 1.5 (0.2–19.5), and 6.0 (0.9–73.6) for the three doses of BI 764198, respectively, and 4.9 (1.0–48.8) for all doses combined. The most notable effect was observed with the 20 mg dose, showing a placebo-corrected reduction in proteinuria of approximately 40%. Importantly, all patients with TRPC6 variants receiving BI 764198 responded to treatment. Estimated GFR and blood pressure remained stable, indicating a direct podocyte-protective mechanism rather than a haemodynamic effect. The drug demonstrated a favorable safety profile, with adverse events comparable to placebo and no significant safety concerns.

Comment. Focal segmental glomerulosclerosis (FSGS) is a glomerular disease marked by podocyte injury, proteinuria, and a high risk of progressing to kidney failure. Modern classification recognizes three main types based on cause: primary, secondary, and genetic. Current treatments for primary and genetic forms are still limited, emphasizing the need for targeted therapies. This study is important because it introduces a mechanistically targeted therapy that tackles podocyte dysfunction, a key factor in FSGS progression. The results support the biological significance of TRPC6 in both genetic and primary forms of the disease and suggest that even partial modulation of channel activity may provide clinical benefits. However, the study has notable limitations, including a small sample size, short follow-up period, variability across dose groups, and relatively normal (non-nephrotic) serum albumin levels in some patients,

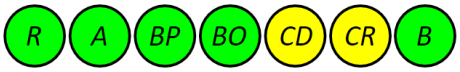
which raises questions about the true prevalence of primary FSGS in the cohort. The unexpected lack of a clear dose–response relationship, along with the superior outcomes of the lowest dose, raises further questions about optimal dosing and pharmacodynamics. Additionally, the short duration prevents conclusions about long-term renal outcomes and safety. Overall, while preliminary, these findings are promising and support the need for larger, longer phase 3 trials to confirm efficacy, determine optimal dosing, and evaluate impacts on kidney function decline.

ISN Academy: ***Glomerular Disease***

Atacicept reduced proteinuria and disease activity markers in high-risk IgA nephropathy in the phase 3 ORIGIN 3 interim analysis

A Phase 3 Trial of Atacicept in Patients with IgA Nephropathy

Lafayette R et al. N Engl J Med. 2026. doi: 10.1056/NEJMoa2510198



Reviewed by Chiara Ruotolo

Summary: This prespecified interim analysis of the ongoing phase 3 ORIGIN 3 trial evaluated atacicept in adults with biopsy-confirmed IgA nephropathy. In this randomized, double-blind, placebo-controlled study, participants were assigned 1:1 to self-administer subcutaneous atacicept 150 mg once weekly or a matching placebo. Eligible patients had either a protein-to-creatinine ratio ≥1.0 on a 24-hour urine collection (both analytes in grams) or total protein ≥1.0 g/day, plus an eGFR ≥30 ml/min/1.73 m², stable maximally tolerated renin–angiotensin system blockade, and controlled blood pressure; stable SGLT2 inhibitor therapy was allowed. The interim efficacy analysis included 203 patients, while the safety analysis included 428 treated patients. Baseline characteristics were comparable between groups. The primary endpoint was the percentage change from baseline to week 36 in the urinary protein-to-creatinine ratio, assessed using 24-hour urine collections. The reduction was 45.7% with atacicept and 6.8% with placebo, corresponding to a geometric mean between-group difference of 41.8 percentage points (95% CI, 28.9 to 52.3; P<0.001). Secondary endpoints at the interim analysis included changes in serum galactose-deficient IgA1 and in hematuria resolution. Galactose-deficient IgA1 decreased by 68.3% with atacicept and 2.9% with placebo, while hematuria resolved in 81.0% and 20.7% of patients with baseline hematuria, respectively (odds ratio, 19.1; 95% CI, 7.3 to 50.0). The exploratory reduction in urinary albumin-to-creatinine ratio was 47.3% with atacicept and 8.8% with placebo. The week 52 eGFR endpoint was not reported in this interim analysis. Adverse events occurred in 59.3% of patients receiving atacicept and 50.0% receiving placebo; most were mild or moderate. Injection-site reactions were more frequent with atacicept, whereas serious adverse events were less common. No deaths or opportunistic infections were reported.

Comment: This trial evaluates a mechanistically targeted therapy in IgA nephropathy that acts upstream in the disease pathogenesis through dual BAFF/APRIL inhibition. This approach reduces the production of pathogenic galactose-deficient IgA1 and the subsequent formation of immune complexes. Consistent improvements in proteinuria, galactose-deficient IgA1 levels, and haematuria support the biological plausibility of the treatment effect. Together, these findings suggest that atacicept may act as a disease-modifying therapy by targeting key immunopathogenic mechanisms, rather than functioning solely as a nonspecific antiproteinuric and immunosuppressive agent. However, despite its methodological strengths, this is a prespecified interim analysis focused on surrogate and biomarker-based outcomes, and kidney function results have not yet been reported. As such, the long-term clinical relevance of these findings will depend on whether the final analysis demonstrates meaningful preservation of kidney function. In addition, the secondary biomarker and haematuria analyses were not adjusted for multiplicity and should therefore be interpreted as supportive rather than definitive. Overall, the study provides strong evidence for targeted immune modulation in IgA nephropathy, but the role of atacicept in routine clinical practice will depend on confirmation of sustained nephroprotective benefits.

ISN Academy: ***Glomerular Disease***

SELUNE Trial: When Biological Plausibility Fails, No Added Benefit of IL-17A Inhibition in Lupus Nephritis

Secukinumab in active lupus nephritis: results from a phase III randomized, placebo-controlled study (SELUNE) and an open-label extension study

Zhao MH et al. Rheumatology (Oxford). 2026. doi: 10.1093/rheumatology/keaf536.

R A BP BO CD CR B

Reviewed by Mohamed Elrgal

Summary: This phase III trial (SELUNE) assessed the effectiveness and safety of secukinumab (an anti–IL-17A monoclonal antibody) at a dose of 300 mg, added to the standard of care (SoC), in adults with active lupus nephritis (LN). The core study was planned for 104 weeks, while the extension study was open-label and intended to last up to 260 weeks. A total of 275 patients were randomized, with the primary endpoint being complete renal response (CRR) at 52 weeks. The study was terminated early after a pre-specified futility analysis indicated no clinically meaningful benefit. At week 52, CRR was numerically lower in the secukinumab group (24.2%) than in the placebo group (36.3%), and no significant differences were observed in secondary outcomes, including partial renal response (PRR), reduction in proteinuria, or patient-reported outcomes. Safety profiles were generally similar between groups, although there was a higher incidence of non-serious fungal infections (notably candidiasis) with secukinumab. The extension study was underpowered (n=31) and produced results that could not be interpreted. Overall, secukinumab did not demonstrate superiority over placebo in LN despite a biologically plausible IL-17–mediated mechanism.

Comment: In this trial, IL-17A inhibition is proposed as a therapeutic approach for lupus nephritis by targeting key inflammatory pathways and potentially reducing kidney damage. However, several limitations affect how the results are interpreted and their relevance beyond the study. First, early termination due to futility reduced statistical power and precluded evaluation of long-term benefits, potentially leading to missed delayed treatment effects and limiting conclusions. Second, the high placebo response rate (36.3%), likely influenced by SoC therapy, may have diminished the apparent treatment effect. Third, the strict definition of CRR (particularly UPCR ≤0.5 mg/mg) might have reduced the study's sensitivity, although secondary outcomes also showed no change. Additionally, pharmacokinetic issues—such as reduced drug exposure caused by proteinuria-driven drug clearance—were not prospectively considered in the dosing strategy, presenting a possible mechanistic confounder. Future research should explore higher doses of secukinumab and evaluate its safety and efficacy in specific lupus nephritis subgroups to identify those who may benefit from IL-17A inhibition.

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

Pravastatin failed to improve kidney volume and function in autosomal dominant polycystic kidney disease patients compared to placebo

A randomized controlled trial evaluated the effect of pravastatin on kidney disease outcomes in adult patients with early-stage autosomal dominant polycystic kidney disease

Gitomer et al. Kidney Int. 2026.doi: 10.1016/j.kint.2025.08.037.

R A BP BO CD CR B

Reviewed by Nicolina Basic-Jukic

Summary: In the present study, 150 patients were randomly assigned to receive 40 mg of pravastatin or a placebo for two years. The primary outcome was the annual percent change in height-adjusted total kidney volume (HtTKV), with secondary endpoints including changes in renal blood flow and GFR (mGFR) measured over the 2-year treatment period. Data from 138 participants were available for analysis. The annual rate of increase in HtTKV median (interquartile range) was 3.1% (1.4, 6.8) in the placebo group and 4.3% (3.0, 6.6) in the pravastatin group. The annual decline in RBF was -15.1 mL/min/1.73 m² (95% CI: -50.7, 14.4) for pravastatin vs. -32.7 mL/min/1.73 m² (95% CI: -62.1, -0.8) for placebo. Median mGFR decline was -1.4 (-6.4, 2.0) for pravastatin vs. -2.3 (-5.1, 1.6) for placebo. Statistical analysis confirmed that neither the primary nor secondary outcomes differed significantly between the treatment arms.

Comment: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder. Tolvaptan remains the only approved disease-modifying therapy, but its use is constrained by aquaretic adverse effects and cost. Preclinical data suggest that statins attenuate cyst growth, and earlier clinical studies have reported improvements in renal blood flow and endothelial function. In the present study, pravastatin did not reduce HtTKV or slow the decline in kidney function compared with placebo. However, several limitations may confound these findings.

Data on urological complications—such as macrohematuria, cyst haemorrhage, and infection—are lacking, despite their established association with accelerated disease progression. Similarly, the absence of information on lifestyle measures limits interpretation, as these factors may influence renal outcomes.
Furthermore, blood pressure targets were defined as <140/80 mm Hg, which is less stringent than currently recommended for ADPKD by the latest KDIGO ADPKD Guidelines, potentially attenuating detectable treatment effects. In addition, the lack of detailed reporting on antihypertensive therapy further restricts assessment of confounding. Future studies should incorporate comprehensive clinical phenotyping, including urological events, lifestyle factors, and detailed therapeutic data, to more accurately define the potential role of statins in ADPKD progression.

ISN Academy: Pediatric Nephrology

Taming the Salt Load: Enhancing Dialysate Sodium Removal in Critically Ill Children with Acute Kidney Injury

Dialytic sodium removal in children with acute kidney injury treated with peritoneal dialysis

Nourse et al. Pediatr Nephrol. 2026. doi: 10.1007/s00467-025-06861-8.

Reviewed by Anastasiia Zykova

Summary: This secondary analysis of a randomized crossover trial evaluates Dialysate Sodium Removal (DSR) for dialysis adequacy in infants (<15 kg, n=15) with Acute Kidney Injury (AKI), comparing conventional Peritoneal Dialysis (PD) to Continuous Flow Peritoneal Dialysis (CFPD). CFPD utilized two 8.5-Fr catheters inserted via the Seldinger technique. Following an initial 20 mL/kg fill (2.5% lactate), continuous flow was established at 50 mL/min/1.73 m², with the outflow rate slightly higher (+2.5 mL/min/1.73 m²) to facilitate ultrafiltration (UF). Every 4 hours, the system was fully drained to calculate UF using the mass difference between the delivery and drainage bags. Findings reveal that while critically ill children receive a massive sodium burden of approximately 14 mmol/kg/day, conventional PD achieved a DSR of only 2.7 mmol/kg/day, significantly lower than the 11 mmol/kg/day previously reported in smaller cohorts. In contrast, CFPD demonstrated a significantly higher DSR, driven primarily by increased ultrafiltration (UF) volumes. Analysis of transport kinetics showed a Dialysate-to-Plasma (D/P) sodium ratio of 0.94 and a Small Pore Ultrafiltration (UFSP) to total UF ratio of 82% in conventional PD (dropping to 66% in CFPD).

Comment: Acute PD remains a crucial, often first-line treatment for AKI in paediatric ICU, especially in resource-limited areas like Africa where extracorporeal therapies may be scarce. This study quantifies a “sodium gap” in critically ill children: with sodium intake of around 14 mmol/kg/day and removal via conventional PD at only 2.7 mmol/kg/day, a significant positive sodium balance occurs, likely leading to extracellular fluid expansion and worse outcomes. The findings also reveal limitations of sodium removal during acute PD and explain them mechanistically. Sodium sieving during short dwell times removes free water via aquaporins with minimal sodium, lowering dialysate sodium concentration. Short cycles (e.g., 1-hour dwells) end before sodium equilibrates through small pores, so the drained fluid remains relatively sodium-poor. Ultrafiltration continues, but net sodium removal drops. CFPD primarily enhances sodium removal by maintaining continuous flow and higher ultrafiltration volumes. The constant dialysate refresh preserves a favourable concentration gradient for water and sodium removal, avoiding the early “sieving” effect of intermittent short dwells. This allows more time and surface area for sodium transport, leading to greater clearance. Despite limitations such as a small sample size and potential measurement inaccuracies from indirect ion-selective electrodes in high-glucose dialysate, the study provides evidence supporting CFPD as a more effective modality for sodium and solute removal. Future research should link improved dialytic sodium removal to clinical outcomes like reduced fluid overload and serum sodium stabilization, to better guide acute PD use.

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