











Global Trials Focus

October-November 2023

The ISN-ACT (Advancing Clinical Trials) team presents the October-November 2023 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

-  Random sequence generation
-  Allocation concealment
-  Blinding of participants/personnel
-  Blinding of outcome assessment
-  Complete outcome data
-  Complete outcome reporting
-  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!

@ISNeducation 

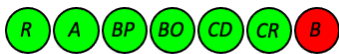
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ENVISION-ing a new way forward in IgA nephropathy

A phase 2 trial of sibeprenlimab in patients with IgA nephropathy

[Mathur et al, N Engl J Med \(2023\).](#)



Reviewed by Daniel V O'Hara

Summary: IgA nephropathy is an autoimmune disease in which there is an overproduction of galactose-deficient IgA1 antibodies which complex with IgG autoantibodies and deposit in the renal mesangium resulting in glomerular injury. IgA production is regulated in part by a proliferation-inducing ligand (APRIL). The humanized monoclonal antibody, sibeprenlimab, is designed to block APRIL activity, thereby potentially attenuating IgA nephropathy activity. In this phase 2 study, 155 adults with biopsy-confirmed IgA nephropathy with eGFR ≥ 30 mL/min/1.73m² and ≥ 0.75 g protein per gram of creatinine daily (or ≥ 1 g proteinuria daily) despite maximum-tolerated dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for at least 3 months were recruited to evaluate the efficacy and safety of different doses of sibeprenlimab. Individuals with nephrotic syndrome or those receiving systemic immunosuppression were excluded, as were those with $>50\%$ tubulointerstitial fibrosis or crescents in $>25\%$ of glomeruli. Participants (median age 39 years, 57% male, 74% Asian) were randomized to 1:1:1:1 to placebo or to sibeprenlimab at 2, 4 or 8mg/kg of body weight, given as monthly infusions for 12 months. At the end of 12 months, the 24-hour urine protein-to-creatinine ratio (uPCR) showed a geometric mean reduction ratio of 20.0 \pm 12.6% with placebo, while there was a statistically significant dose-dependent beneficial trend to this ratio of 47.2 \pm 8.2%, 58.8 \pm 6.1% and 62.0 \pm 5.7% with sibeprenlimab at 2-, 4- and 8-mg/kg, respectively ($p < 0.001$ for linear treatment effect). The least-squares mean (\pm SE) change in eGFR from baseline was -7.4 ± 1.8 mL/min/1.73m² with placebo, and -2.7 ± 1.8 , 0.2 ± 1.7 , and -1.5 ± 1.8 mL/min/1.73m² with the 2-, 4- and 8-mg/kg sibeprenlimab doses, respectively. There were no concerning safety signals including infections or lymphopenia between the placebo or pooled sibeprenlimab groups.

Comment: IgA nephropathy is the most common form of glomerulonephritis worldwide and is associated with significant progression to kidney failure despite current treatment standards. The ENVISION study suggests that sibeprenlimab may provide a potent new treatment option, particularly at the 4mg/kg and 8mg/kg doses, which have shown stabilization of eGFR and a greater reduction in uPCR as compared to placebo, with sustained benefits in proteinuria even at 5 months after discontinuation. The results of this phase 2 trial should be interpreted with caution, particularly as there were some imbalances in baseline characteristics that may have predisposed those receiving placebo to a higher risk of progression, including a higher mean percentage of crescents and longer time since diagnostic kidney biopsy. Moreover, those in the placebo group had a higher proportion of females and were

ISN Academy: [Glomerular Diseases](#)



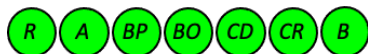
relatively younger than patients in the sibeprenlimab groups, and the impact of this on the progression of IgA nephropathy is uncertain. Further efficacy and safety results of the ongoing phase 3 trial (NCT05248646) will be eagerly awaited.

ISN Academy: [Dialysis](#)

Upacicalcet: A novel injectable calcimimetic shows promise in controlling secondary hyperparathyroidism in the hemodialysis population

Efficacy and safety of upacicalcet in hemodialysis. Patients with secondary hyperparathyroidism; a randomized placebo-controlled trial

[Shigematsu et al, Clin J Am Soc Nephrol, \(2023\).](#)



Reviewed by *Ahad Qayyum*

Summary: This multi-center study randomized 153 participants on chronic hemodialysis with a serum intact PTH (iPTH) of >240pg/ml and corrected calcium concentrations ≥ 8.4 mg/dL in a 2:1 ratio to either receive upacicalcet (a novel intravenous calcimimetic) or placebo after each dialysis session over a 24 week study period. Of the 103 participants randomized to receive upacicalcet, 67% (69/103) attained the target mean serum iPTH concentration of 60-240pg/ml, whilst only 8% (4/50) achieved this target level in the placebo group. The difference in proportions between the two groups was 59% (95% confidence interval (CI), 48% to 71%, $P < 0.001$). Upacicalcet also significantly decreased serum fibroblast growth factor-23, bone-specific alkaline phosphatase, total type 1 procollagen-N-propeptide, and tartrate-resistant acidphosphatase-5b concentrations, which can be elevated in the context of abnormal bone turnover. From a safety perspective, there was no statistically significant difference in adverse events between the upacicalcet and placebo groups (85% vs 72%, $P = 0.076$), including gastrointestinal issues such as nausea and vomiting, and upacicalcet did not induce symptomatic hypocalcaemia.

Comment: Calcimimetics are considered effective in controlling intact parathyroid hormone levels in the dialysis population but also have gastrointestinal and hepatic side effects, which may limit their tolerability and therefore uptake. The use of upacicalcet in this study shows promise in managing secondary hyperparathyroidism and its associated hormonal and metabolic laboratory abnormalities with potentially fewer side effects in patients on hemodialysis. However, given this study is placebo-controlled, further studies are required to confirm non-inferiority or superiority to other calcimimetics like cinacalcet. It's worth noting that this study's findings may not be generalisable as only Japanese hemodialysis patients were included, and it is common practice to target lower serum iPTH levels in Japan than recommended in the KDIGO guidelines. Therefore, further studies encompassing diverse ethnic groups and populations are needed.

ISN Academy: [Transplant](#)

Precision medicine: revolutionizing tacrolimus dosing for kidney transplant recipients with model-based Bayesian Prediction

A prospective controlled, randomized clinical trial of kidney transplant recipients developed personalized tacrolimus dosing using model-based Bayesian Prediction

[Loberas et al, Kidney Int, \(2023\).](#)



Reviewed by *Chiara Ruotolo*

Summary: This open-label, single centre, superiority trial evaluated two dosing methods for tacrolimus immediately after kidney transplantation. One group utilized a population pharmacokinetic model (PPK, $n = 46$) that determined the initial tacrolimus dose based on pharmacogenetics (CYP3A metabolizer phenotype) and age. In this group the tacrolimus dose was subsequently adjusted using a Bayesian prediction model that took into account hematocrit, previous trough tacrolimus levels, genetics and age, to achieve a trough tacrolimus target concentration of 6-10 ng/ml. The control group ($n = 50$) followed conventional body-weight dosing according to the manufacturer's labelling and dose was adjusted based on previous trough tacrolimus levels as per routine clinical practice. A higher proportion of patients in the PPK group achieved the tacrolimus therapeutic target in the first steady state compared with the control group (54.8% vs 20.8%, $P = 0.0011$). After 90 days of follow up, participants in the PPK group had achieved the therapeutic target concentration levels faster than in the control group (5 days [interquartile range (IQR) 5-10] vs 10 days [IQR 10-30], $P < 0.001$), had lower intra-patient variability (24.7 vs 35.8, $P < 0.0001$), had fewer dose modifications (1 vs 2.6, $P < 0.0001$), and a lower percentage of participants had overexposure to tacrolimus. No

differences between the groups were observed in terms of clinical outcomes including biopsy-proven acute rejection, renal function, delayed graft function, graft loss, new onset diabetes after transplantation nor tremor.

Comment: Tacrolimus dosing after kidney transplantation poses challenges as patients are often under- or overexposed during the early post-transplant period, increasing risk of complications such as acute rejection, nephrotoxicity and reduced renal function. High tacrolimus levels can also indirectly lead to persistence of acute tubular necrosis and delayed graft function. Empirical tacrolimus dosing based on the patient's body weight fails to account for significant variations caused by genetic differences, drug interactions, patient-specific factors, and physiological changes, necessitating personalized dosing and vigilant monitoring. This pragmatic trial assessed a population pharmacokinetic (PPK) model integrating multiple variables, and showed that dosing with this model could reach the target tacrolimus concentration rapidly and that it remains stable over time, with fewer dose modifications and lower intra-patient variability, although there were no significant differences in clinical outcomes. Notably, this study did not consider variations in metabolism of tacrolimus between males and females in their model. Replication and validation across diverse populations, including variations in pharmacokinetics based on sex, would provide further support for its feasibility and usefulness.

ISN Academy: [Transplant](#)

Eplerenone administration may blunt the progression of kidney impairment in children with chronic allograft nephropathy

Long-term effect of eplerenone treatment in children with chronic allograft nephropathy

[Baskin et al, *Pediatr Transplant*, \(2023\).](#)



Reviewed by Nikolina Basic-Jukic

Summary: In this single-center, open-label trial, 26 kidney transplant children (aged <18 years) with biopsy-proven chronic allograft nephropathy at least one year after transplantation, with an eGFR >40 mL/min/1.73m², and significant proteinuria (24 hour urine protein >2g/L) despite maximally tolerated renin angiotensin aldosterone system inhibition, were randomized into two groups: one received 25 mg/day eplerenone (n=10) and the other did not receive eplerenone (n=16) for 36 months. At the end of the study period, participants treated with eplerenone maintained a stable mean eGFR (59.2 ± 9.70 vs 57.53 ± 7.53), whilst those who did not receive eplerenone had significantly decreased eGFR (66.40±8.20 vs 44.94±8.04, p <0.001). Additionally, eplerenone-treated participants had a significant reduction in uPCR (2.25 ± 5.68 vs 1.02 ± 7.53), whilst those who did not receive eplerenone had notably higher proteinuria (1.93 ± 0.76 vs 3.61 ± 0.53; p <0.001). Eplerenone treatment was not associated with development of hyperkalemia throughout the study period.

Comment: Chronic allograft nephropathy (CAN) is a leading cause of kidney allograft loss beyond the first year, however there is no specific treatment for this poorly understood entity. Mineralocorticoid receptor antagonists (MRAs) have pleiotropic effects that may potentially improve both short and long-term allograft function. This study showed stabilization of eGFR and reduction of proteinuria in pediatric patients with CAN using eplerenone. However, this study is essentially an exploratory, proof of concept study, and not generalisable given that it is a single centre study, with a small highly selected treatment group. Larger trials are required to confirm the efficacy of MRAs in this specific population, and should include patients with a lower eGFR, with follow-up of not only the effects of eplerenone on kidneys, but also on heart structure and function.

ISN Academy: [Pediatric nephrology](#)

Eculizumab failed to improve early renal outcomes in pediatric STEC-HUS

Efficacy and safety of eculizumab in pediatric patients affected by shiga toxin-related hemolytic and uremic syndrome: a randomized, placebo-controlled trial

[Garnier et al, *JASN*, \(2023\).](#)



Reviewed by Nikolay Bulanov

Summary: Shiga toxin-related hemolytic uremic syndrome (STEC-HUS) is a serious condition affecting children, resulting in the need for kidney replacement therapy in about 50% of cases, with approximately one-third experiencing renal sequelae. The transient activation of the complement alternative pathway in STEC-HUS is potentially a mechanism behind target organ damage. While eculizumab has effectively reversed this activation in atypical hemolytic uremic syndrome (aHUS), its application in treating STEC-HUS has not been tested in a randomised controlled trial setting. In this phase 3 placebo-controlled, patient-blinded trial, 100 pediatric patients

with STEC-HUS (defined by the presence of thrombotic microangiopathy, acute kidney failure with eGFR <75mL/min/1.73m², and prodromal diarrhea and/or presence of an enterohemorrhagic strain of E. coli and/or identification of the Stx 1 or 2 genes) were randomized to receive either eculizumab (n=50) or placebo (n=50). Participants with severe multiorgan damage (i.e. neurological, cardiac, or digestive involvement) at diagnosis were excluded. Moreover, the study explicitly forbade the use of plasma therapy, rituximab and IV immunoglobulin treatment. The primary endpoint of duration of kidney replacement therapy after randomization of less than 48 hours did not differ significantly between the eculizumab (38%) and the placebo groups (48%, P=0.31). However, the proportion of participants experiencing renal sequelae such as hypertension, decreased eGFR and/or proteinuria at 1 year was significantly lower in the eculizumab group (43%) than in the placebo group (64%, P=0.04). The rate of adverse events was comparable in both groups.

Comment: In the ECULISHU trial, eculizumab, a C5 component antagonist, which is recognized as gold standard therapy for aHUS, did not convincingly demonstrate improvement in kidney outcomes during the acute phase of STEC-HUS. Although the rate of renal sequelae at 1 year was lower in the eculizumab group, this outcome should be interpreted with caution due to the limited follow-up. Another limitation of the study is that patients with severe STEC-HUS and multi-organ involvement, in whom eculizumab treatment might have been beneficial, were not included due to ethical considerations of potentially withholding treatment in a critical situation. Despite these non-significant results on the primary endpoint, given the small sample size, lack of harm demonstrated with treatment, and interesting results for secondary outcomes, larger trials with longer follow-up periods are required to more thoroughly evaluate the effectiveness of complement-blocking agents in managing STEC-HUS.

Edited by Daniel V O'Hara, Neeru Agarwal, Michele Provenzano, and Anastasiia Zykova