



Global Trials Focus

February - March 2024

The ISN-ACT (Advancing Clinical Trials) team presents the January 2024-February 2024 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!

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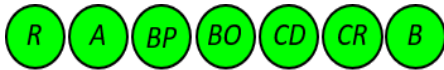
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ISN Academy: [Chronic Kidney Disease](#)

Part of the CKD tool kit? Novel aldosterone synthase inhibitor, BI 690517, reduced albuminuria alone and with empagliflozin, alongside RAS inhibition

Efficacy and safety of aldosterone synthase inhibition with and without empagliflozin for chronic kidney disease: a randomised, controlled, phase 2 trial

[Tuttle, K.R et al., Lancet \(2024\); 403:379-390.](#)



Reviewed by Neeru Agarwal

Summary: BI 690517 is a potent and highly selective inhibitor of aldosterone synthase that directly lowers aldosterone production, potentially slowing the progression of chronic kidney disease (CKD) by decreasing kidney inflammation and fibrosis. This phase 2, placebo-controlled, double-blind study evaluated the efficacy and safety of various oral doses of BI 690517 alone or combined with empagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT-2i), in participants with CKD (eGFR 30-90ml/min/1.73m²) regardless of diabetes status and with a urine albumin to creatinine ratio (uACR) between 200-5000mg/g, and serum potassium ≤4.8mmol/L, who were on stable renin-angiotensin system inhibitor (RASi) therapy. Participants were initially randomised (n = 714, 1:1) to 10mg empagliflozin or placebo for 8 weeks, followed by a second randomisation (n = 586, 1:1:1:1) for 14 weeks with BI 690517 treatment at doses 3mg, 10mg or 20mg daily, or placebo. The percentage change in first morning void uACR from baseline (second randomisation) to week 14 was -3% (95% CI -19 to 17) with placebo, -22% (-36 to -7) with BI 690517 3 mg, -39% (-50 to -26) with BI 690517 10 mg, and -37% (-49 to -22) with BI 690517 20 mg monotherapy. Similar uACR reductions were observed when BI 690517 was added to empagliflozin (-11%, -19%, -46% and -40% for placebo, 3mg, 10mg and 20mg BI 690517 doses, respectively). Of note, among participants receiving the BI 690517 10mg dose, 51% achieved a uACR reduction of ≥30% on monotherapy (OR vs. placebo 6.09; 95% CI 2.64-14.08) and 70% achieved this reduction with empagliflozin added to BI 690517 (OR vs. placebo 8.42; 3.73-19.02). In terms of safety, BI 690517 had an acceptable safety profile. Although there was a dose-dependent increase in hyperkalaemia compared to placebo, most cases did not require medical intervention or discontinuation of the drug, and this increase was possibly reduced in the presence of empagliflozin.

Comment: The current treatment landscape for slowing the progression of CKD includes the use of RASi and SGLT-2i. Furthermore, newer non-steroidal mineralocorticoid receptor antagonists (nsMRAs) have been shown to provide additional cardiac and kidney protection in individuals with diabetic kidney disease. BI 690517 has a different mechanism of action to RASi and nsMRAs, in that it directly lowers aldosterone production. In this context, this trial uniquely shows the additive benefit of combination therapy in CKD by initially having a run-in period and randomising individuals to SGLT-2i in addition to RASi. The trial then goes on to demonstrate clinically meaningful placebo-corrected reductions in microalbuminuria of up to 37-40% on BI 690517 treatment with dose-response

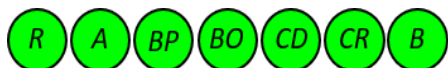
plateauing at 10mg, regardless of empagliflozin use. This trial is however limited by its brief follow-up of only 14 weeks, which may restrict the understanding of the safety of this new drug, and also the study population was predominantly White and male and excluded patients who were eligible for MRAs, limiting its generalisability. Nevertheless, this drug warrants further study in a large phase 3 trial to assess long-term kidney and cardiac benefits, and comparative effectiveness studies comparing nsMRAs with aldosterone synthase inhibitors in CKD might provide better guidance on when to initiate such treatments.

ISN Academy: [Glomerular Diseases](#)

Avacopan and rituximab – a promising combination for patients with ANCA-associated vasculitis.

Efficacy and safety of avacopan in patients with ANCA-associated vasculitis receiving rituximab in a randomised trial

[Gettha et al. Ann Rheum Dis. 2024;83\(2\):223-232.](#)



Reviewed by Nikolay Bulanov

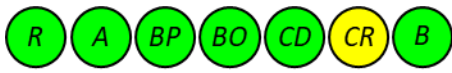
Summary: This study analysed a subgroup of 214 participants with a mean age of 59.8 years, 51.4% female and 86% White and ANCA-associated vasculitis who received induction therapy with rituximab (RTX) every 4 weeks in the double-blind, active-controlled trial, ADVOCATE. In addition to RTX, 107 patients received C5a receptor antagonist, avacopan (30mg twice daily) with placebo-prednisone taper, and 107 received prednisone (60mg/day tapered to 0mg by week 21) with a matching placebo drug. Among these participants, 76.2% had renal vasculitis and 58.4% were newly diagnosed. The efficacy outcomes were remission by week 26 (defined as a Birmingham Vasculitis Activity Score (BVAS) of 0 without corticosteroid treatment in the preceding 4 weeks) and sustained remission (defined as maintaining remission at both weeks 26 and 52, with no corticosteroid treatment in the 4 weeks before week 52, and no relapse between weeks 26 and 52). The majority of the avacopan group achieved remission at week 26 (83/107; 77.6%) and sustained remission at week 52 (76/107; 71%), while the prednisone taper group had remission rates of 75.7% (81/107) at week 26 and sustained remission at week 52 of 56.1% (60/107). Following remission (BVAS of 0) at any time, the avacopan group showed a decreased relapse rate (9/107; 8.7%) in contrast to the prednisone taper group (21/107; 20.2%), with a reduction of relapse risk of 58% (HR 0.42, 95% CI, 0.19 to 0.91). The recovery of kidney function and improvement in urinary albumin to creatinine ratio also favoured the avacopan group. The rate of serious adverse events was similar in the avacopan (34.6%) and prednisone taper groups (39.3%), however, glucocorticoid-induced toxicity (as assessed by the Glucocorticoid Toxicity Index) was greater in the prednisone taper group than in the avacopan group.

Comment: Despite low incidence, with an estimated global pooled incidence (95% CI) of 17.2 per million person-years (13.3–21.6), ANCA-associated vasculitis (AAV) is the most common cause of rapidly progressive glomerulonephritis in adults. For more than a decade, the combination of glucocorticoids and either cyclophosphamide (CYC) or rituximab has remained the standard of care; however, these regimens are associated with significant treatment-related toxicity, thus there is a need for new therapeutic agents. The efficacy and safety of avacopan in combination with RTX or CYC for the induction therapy of AAV has been previously demonstrated in the randomized trials CLEAR and ADVOCATE, leading to the inclusion of the drug in the updated EULAR 2022 and KDIGO 2024 guidelines. This subgroup analysis of the ADVOCATE trial re-confirms the efficacy and safety of avacopan-RTX combination to induce and sustain remission in patients with AAV, including those with kidney involvement. It should be noted that the results have limited generalizability, because the patients did not receive repeat maintenance dosing of RTX at week 26 as recommended in current international guidelines, and participants with baseline eGFR <15 mL/min/1.73 m² and/or alveolar hemorrhage on mechanical ventilation were not included. Further evidence is needed to evaluate the role of Avacopan in this rare condition.

ISN Academy: [Chronic Kidney Disease](#)

Anti-inflammatory therapy may have a potential role in improving hemoglobin levels and iron hemostasis in CKD 3-5

Effect of Ziltivekimab on Determinants of Hemoglobin in Patients with Chronic Kidney Disease Stage 3-5. An Analysis of a Randomized Trial [RESCUE]



Reviewed by *Nayef Habashi*

Summary: This double-blind, placebo-controlled phase 2 trial compared the effectiveness and safety of different doses of ziltivekimab (an IL-6 ligand antibody) versus placebo on changes in haemoglobin and biomarkers of iron homeostasis in patients with CKD stages 3-5 (eGFR >10 and <60ml/min/1.73m²) and high-sensitivity C-reactive protein (hs-CRP) ≥2mg/L. 264 participants were randomised (1:1:1:1) to subcutaneous ziltivekimab (7.5mg, 15mg, or 30mg), or placebo once every 4 weeks. The mean age of participants was 66.4 years, 49% were women and the mean hemoglobin was 12.2-12.5g/dL. Ziltivekimab was associated with a significant increase in hemoglobin level from baseline to week 12 when compared to placebo. The mean change in hemoglobin from baseline to week 12 were -0.22g/dL for placebo and +0.34, +0.82, and +0.77 for ziltivekimab 7.5mg, 15mg, 30mg, respectively, corresponding to treatment difference versus placebo of +0.57 g/dL (95% CI, 0.27-0.86, P<0.001), +1.05 g/dL (95% CI, 0.76 -1.33, P<0.001), and +0.99 g/dL (95% CI, 0.70- 1.28, P<0.001), respectively. Differences in hemoglobin between the ziltivekimab and placebo groups could be observed as early as week 1. Ziltivekimab also led to notable rises in serum iron levels, total iron binding capacity and transferrin saturation compared to placebo across all doses. Reticulocyte hemoglobin levels increased significantly in the 15mg and 30mg ziltivekimab treatment groups only. However, ferritin and hepcidin levels showed no significant changes across the ziltivekimab treatment groups. Also, lower baseline transferrin saturation quartiles correlated with higher hs-CRP levels, indicating inflammation's role in reducing bioavailable iron for hematopoiesis. However, ziltivekimab's use potentially improved iron availability by mitigating inflammation, as evidenced by lower hs-CRP levels and higher transferrin saturations. Ziltivekimab exhibited good tolerability, with no significant safety issues identified.

Comment: Ziltivekimab could offer a new therapeutic approach to treating anemia in patients with CKD who often have high levels of inflammation. By treating inflammation, this agent has the potential to increase hemoglobin without the need for erythrocyte-stimulating agents (ESAs) or iron therapies. Interestingly, transferrin saturation, rather than ferritin, may serve as a more reliable indicator of iron availability for erythropoiesis during inflammatory conditions. Despite the positive short-term results of ziltivekimab, the long-term outcomes are still not known as the study was terminated earlier than expected because of the onset of the COVID-19 pandemic and the concern that an exogenous cause of CRP increases in the general population could skew the study results. Also, most patients had baseline hemoglobin levels >11g/dL and no patient was on an ESA. Therefore, the effects of ziltivekimab on ESA dosage in CKD remain to be determined. The ongoing phase 3 trial, ZEUS, also assessing cardiovascular outcomes with ziltivekimab (15mg) compared to placebo in 6200 stage 3–4 CKD patients with elevated hs-CRP levels, will answer some of these questions.

ISN Academy: [Transplant](#)

Protocols with early steroid withdrawal or tacrolimus minimization are non-inferior to standard immunosuppression for kidney transplant function at two years

Comparison of 2 Immunosuppression Minimization Strategies in Kidney Transplantation: The ALLEGRO Trial

[van den Born et al. Transplantation. 2024;1;108\(2\):556-566.](#)



Reviewed *Nikolina Basic-Jukic*

Summary: In this 24-month, open-label, multicenter trial, a total of 295 kidney transplant recipients 68% male, mean age 56.4 years, with low to medium immunological risk, were randomly assigned to one of three treatment groups: early steroid withdrawal, standard-dose tacrolimus, or tacrolimus minimization. All participants received standard induction with Basiliximab (day 0 + 4), methylprednisone (days 0-2) and mycophenolate sodium. Participants in the early steroid withdrawal group received no maintenance prednisolone from day 3 post-transplantation, while those in the standard-dose tacrolimus and tacrolimus minimization group received 10mg prednisolone daily for the first 6 weeks, tapered to 7.5mg for the remainder of the study. Participants in the standard-dose tacrolimus group received extended-release tacrolimus once daily with target trough levels of 8-12ng/mL for the first 6 weeks and 6-10ng/mL for the remainder of the study. Those in the tacrolimus minimization group had target trough levels lowered to 3–5 ng/mL starting from 6 months after transplantation. In the intention-to-treat analysis, the study demonstrated noninferiority for the primary endpoint; the eGFR at 24 months was 45.3mL/min/1.73m² in the early steroid withdrawal group, 49.0 mL/min/1.73 m² in the standard

immunosuppression group, and 44.7 mL/min/1.73 m² in the tacrolimus minimization group. However, participants in the early steroid withdrawal group were more often treated for rejection (23/71; 23.5%) compared to the standard immunosuppression (14/74; 14%) and tacrolimus minimization group (11/74; 11.3%) (log-rank test; P=0.04). Moreover, eGFR at 24 months significantly differed among participants with treated rejection (35.4 mL/min/1.73 m²) compared to those without treated rejection (48.1 mL/min/1.73 m²; P = 0.001). Despite this, those in the early steroid withdrawal group exhibited a more favourable cardiovascular risk profile with lower total cholesterol and a reduced incidence of diabetes mellitus 24 months post-transplantation.

Comment: Despite the excellent short-term results of kidney transplantation, the long-term outcomes remain suboptimal. In addition to immunological events that influence kidney allograft survival, morbidity and mortality are increased due to infections, malignancies, and cardiovascular complications. While immunosuppressive medications largely contribute to these risks, the optimal maintenance treatment regimen after kidney transplantation to mitigate these risks remains limited. Therefore, advancements in understanding the potential benefits and complications associated with different immunosuppressive protocols are essential. Steroids are recognized for exacerbating cardiovascular risk including increased likelihood of diabetes, dyslipidemia, and hypertension, while tacrolimus heightens the risk of diabetes and nephrotoxicity. This study describes that tacrolimus minimization with lower target trough levels is as safe and effective as standard tacrolimus levels with regards to graft function and rejection rates, and can be considered in kidney transplant recipients with low immunological risk. Although early steroid withdrawal offers notable metabolic advantages, it also increases the risk of rejection. Thus, the decision to withdraw steroids should be carefully considered. A major limitation of the study is that it was powered to show non-inferiority on the primary endpoint therefore may be underpowered to compare other outcomes such as biopsy-proven acute rejection and cardiovascular outcomes. The generalizability of non-inferiority trials may be limited by the strict inclusion criteria and may not reflect real-world practice patterns, potentially undermining their applicability to broader patient populations and clinical settings. Moreover, the 24-month follow-up period may not suffice to accurately assess the effectiveness of maintenance immunosuppression post-transplantation. Future studies should extend the follow-up duration to better ascertain the advantages and potential complications associated with different immunosuppression minimization strategies.

ISN Academy: [Dialysis](#)

SLEEP-HD Trial Results: The quest continues for an effective therapy for insomnia in hemodialysis patients

Effectiveness of Existing Insomnia Therapies for Patients Undergoing Hemodialysis A Randomized Clinical Trial.
[Mehrotra et al. Ann Intern Med. 2024;177\(2\):177-188.](#)



Reviewed by *Bassem Tanios*

Summary: In this multicenter, placebo-controlled trial, 126 patients undergoing 3x/week community-based hemodialysis (HD) who suffered from mild to moderate insomnia, defined as having an Insomnia Severity Index (ISI) score ≥ 10 and reported sleep disturbance for ≥ 3 nights/week for 3 months, were included. Participants were randomly assigned to three groups in a 1:1:1 ratio: Telehealth cognitive-behavioural therapy (30 minutes weekly via Zoom) for insomnia (CBT-I), trazodone 50-100mg, or placebo for 6 weeks. About half the patients were female and 20% were Black, which differs from the United States Renal Data System (USRDS) population, which typically comprises a higher proportion of Black individuals. At week 7, the change in the primary outcome of ISI score from baseline was similar among the three groups. The CBT-I group showed a change of -3.7 (95% CI, -5.5 to -1.9), the trazodone group showed a change of -4.2 (95% CI, -5.9 to -2.4), and the placebo group showed a change of -3.1 (95% CI, -4.9 to -1.3) (P=0.68). At week 25, there was also no significant difference in ISI score from baseline among the three groups. The CBT-I group showed a change of -4.8 (95% CI, -7.0 to -2.7), the trazodone group showed a change of -4.0 (95% CI, -6.0 to -1.9), and the placebo group showed a change of -4.3 (95% CI, -6.4 to -2.2) (P=0.84). The trazodone group had an increased risk of serious adverse events (SAEs) due to cardiac causes, even in those with no history of ischemic heart disease. The annualized cardiovascular SAE incidence rates were 0.05 (95% CI, 0.00 to 0.29) for CBT-I, 0.64 (95% CI, 0.34 to 1.10) for trazodone, and 0.21 (95% CI, 0.06 to 0.53) for placebo.

Comment: Chronic insomnia is a common problem in patients undergoing long-term HD, affecting almost 50% of patients. Insomnia can negatively influence the quality of life, and increase the risk of blood pressure variability and mortality in these patients. Therefore, it is essential to find safe interventions, whether non-pharmacologic or pharmacologic, to improve insomnia. In this randomized clinical trial, the effectiveness of CBT-I, trazodone, and placebo were compared. The results showed that neither CBT-I nor trazodone was more effective than placebo, and trazodone was associated with harm. It is understandable that trazodone, a serotonin antagonist and reuptake inhibitor approved for depression treatment but commonly used off-label for insomnia, did not prove effective in addressing sleep issues. Further, trazodone blocks alpha-adrenergic receptors and this may explain the known adverse cardiac effects (QT prolongation, torsades and orthostatic hypotension). Despite this being the largest RCT addressing sleep in HD patients, using validated scores as outcomes, this trial had several limitations. The study mainly included patients with mild or moderate chronic insomnia, therefore, the findings may not apply to patients with severe insomnia; the CBT-I arm could inherently not be blinded; and the trial interventions were short-term (only for six weeks). Therefore, further rigorous research testing a wide variety of interventions is warranted to develop a much-needed effective therapy for insomnia in dialysis patients.

ISN Academy: [Dialysis](#)

Solace from the SPIRIT: Advance Care Planning can help dialysis patients and their surrogates handle emotional distress

Effectiveness of an Advance Care Planning Intervention in Adults Receiving Dialysis and Their Families A Cluster Randomized Clinical Trial

[Song et al. JAMA Netw Open. 2024; 7\(1\): e2351511](#)



Reviewed by Maria Maawad

Summary: The Advance Care Planning Program SPIRIT (Sharing Patients' Illness Representations to Increase Trust) was designed to better understand the needs of haemodialysis patients and to prepare surrogates for their role. In this pragmatic cluster-designed clinical trial 42 medical centers in the US participated to assess whether such a program could be beneficial versus usual care for the patient-surrogate dyad. In total, 231 dyads were enrolled in the experimental arm and 195 were enrolled in the control arm. The intervention included a 45-60 minute advance care planning discussion with the dyads face-to-face or remotely. A second optional short session was conducted 2 weeks later to discuss any concerns. These sessions were conducted by a certified practitioner (e.g. nurse practitioner, registered nurse, or social worker). After 2 weeks, dyads in the experimental group had higher congruence regarding goals-of-care (OR 1.61; 95% CI, 1.12-2.31; P=0.001), lower decisional conflict (β -0.10; 95% CI, -0.13 to -0.07; P < 0.001) and higher frequency of positive composite outcomes, i.e. combining dyad congruence and surrogate decision-making confidence (OR, 1.57; 95% CI, 1.06-2.34; P =0.03) compared with the controls. During follow-up, 54 participants in the intervention group and 35 in the control group died. Three months after the participants' death, surrogates in the experimental arm had a lower anxiety score (β , -1.55; 95% CI, -3.08 to -0.01; P=0.05) compared to the control surrogates, but there were no significant differences in depression and post-traumatic distress scores.

Comment: Advance Care Planning previously centred on completing advance directives or supporting family decision-making near the end of life in acute care settings. However, these efforts often overlooked the profound emotional distress experienced by patients and their families. In response, the SPIRIT intervention sought to assist patients and their surrogate decision-makers in collaboratively preparing for EOL decision-making, aiming to enhance both the decision-making process and surrogate bereavement outcomes. This is the largest trial conducted to date in different regions of the US which has shown positive effects on dyad preparation and surrogate bereavement after SPIRIT delivery. Notably, unlike [previous research](#), this study found insignificant effects on depression and posttraumatic symptoms, possibly attributed to the distress caused by the COVID-19 pandemic. Further studies could be conducted to verify the beneficial effects of the SPIRIT programme on the long-term outcomes of dialysis patients' family members and partners in other parts of the world.

However, implementing such a program faces challenges such as ensuring widespread acceptance among patients and healthcare providers, addressing cultural and linguistic diversity, integrating with existing healthcare systems, and sustaining long-term engagement. Scalability may be hindered by resource constraints, technological infrastructure requirements, and the need for standardized protocols adaptable across diverse care settings.

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