Global Trials Focus August - September 2024

The ISN-ACT (Advancing Clinical Trials) team presents the May-June 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

- (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

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ISN Academy: Acute Kidney Injury

Amino Acid infusion for AKI prevention is more hype than hope

A Randomized Trial of Intravenous Amino Acids for Kidney Protection, The PROTECTION Randomized Clinical Trial

Landoni G. et al., 2024. NEJM. 2024 Aug 22;391(8):687-698.

R A BP BO CD CR B

Reviewed by Mohamed Elrggal

Summary: The PROTECTION trial was a double-blind, multinational study (in 22 centers in three countries Italy, Singapore, Croatia) involving 3,511 adult patients scheduled for cardiac surgery with cardiopulmonary bypass. The trial aimed to determine whether intravenous infusion of amino acids (2g/kg/day) could reduce the occurrence of postoperative AKI. Those with eGFR <30 ml/min/1.73 m^2 and those on or scheduled for kidney replacement therapy (KRT) were excluded. 1759 patients were randomly assigned to the amino acid group and 1752 to the placebo group. The trial population was predominantly White, with a median age of 66 and 30% female participation. Most had moderate heart failure (NYHA class II/III) and an LVEF of around 60%. Diabetes was present in fewer than 20%, and 40% were on statins. About 35% had CABG, while others had valve surgeries, with some undergoing both. Requirements for intraoperative inotropes, vasoactive drugs and loop diuretics were similar in both groups. Those randomized to amino acids received them via a continuous infusion at a specific dosage until one of several endpoints (72 hours, ICU discharge, KRT, or death), with adjustments based on concurrent nutrition. The solution had specific osmolarity and pH values. The primary outcome, the occurrence of AKI within the first week after surgery, was reached in 26.9% of patients receiving amino acids, compared to 31.7% in the placebo group, demonstrating a relative risk reduction of 15% (RR 0.85; 95% CI, 0.77 to 0.94; P=0.002). The study also found a smaller but significant reduction in severe (stage 3) AKI in the amino acid group (RR 0.56; 95% CI, 0.35 to 0.87), with no difference in adverse events, the need for and the duration of KRT, hospital length of stay (LOS), or 30- and 180-day mortality rate. The authors concluded that intravenous amino acid therapy could serve as an effective intervention to reduce AKI in patients undergoing cardiac surgery.

Comment: Amino acid infusion is hypothesized to protect against AKI by improving renal perfusion and recruiting renal functional reserve. While the study reports a notable 5% absolute and 15% relative risk reduction in stage 1 AKI, along with a 1.4% absolute and 44% relative risk reduction in stage 3 AKI, it is

important to note that the difference in clinical outcomes like the need for KRT, hospital LOS, mortality and other clinically relevant outcomes were not significant. The study exclusively used serum creatinine levels to define AKI, a standard but somewhat limited marker. Considering the advances in AKI biomarkers, the tubular damage biomarkers like neutrophil gelatinase-associated lipocalin (NGAL) or kidney injury molecule 1 (KIM-1) should have been reported. Additionally, 336 patients underwent hemofiltration as part of the bypass surgery center protocol, which further complicate how to interpret post-operative serum creatinine levels. The patient population was predominantly from high-income countries, which may limit the generalizability of the findings to low- and middle-income settings where the baseline risk and management of AKI may differ significantly. The study's exclusion of patients with more advanced CKD further restricts the applicability of the findings to higher-risk groups.

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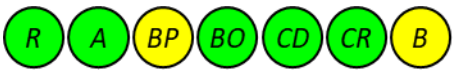
*ISN Academy: **Transplant***

Bleselumab failed to prevent biopsy-proven recurrence of FSGS after kidney transplantation

Efficacy and Safety of Bleselumab in Preventing the Recurrence of Primary Focal Segmental Glomerulosclerosis in Kidney Transplant Recipients: A Phase 2a, Randomized, Multicenter Study

Shoji J et al. Transplantation 2024;108: 1782–1792.



Reviewed by Nikolina Basic-Jukic

Summary: Bleselumab (ASKP1240) is a novel, fully human immuno-globulin G4 anti-CD40 antagonistic monoclonal antibody that displayed a dose-dependent, prolonged occupancy of B-cell CD40 receptors in a phase 1b study in de novo kidney transplant recipients. In this phase 2a, multicenter, open-label study 63 adult recipients of a living or deceased donor kidney transplant with a history of biopsy-proven primary FSGS were randomized to bleselumab combined with tacrolimus and corticosteroids versus standard of care (SOC) including tacrolimus, mycophenolate mofetil, and corticosteroids as maintenance immunosuppression in the prevention of recurrent FSGS (rFSGS) >12 months post transplantation. All patients received basiliximab induction. Bleselumab was initiated intraoperatively before revascularization. It was administered over 30 min as a 200-mg intravenous infusion on days 0, 7, 14, 28, 42, 56, 70, and 90, and monthly after that. All patients who did not have a biopsy with a diagnosis of rFSGS by 3 months posttransplant had a protocol-defined biopsy at the day 90 visit. The primary endpoint was rFSGS, defined as proteinuria (protein-creatinine ratio ≥3.0 g/g) with death, graft loss, or loss to follow-up imputed as rFSGS, through 3 months posttransplant. The relative decrease in rFSGS occurrence through 3 months with bleselumab versus SOC was 40.7% (95% confidence interval, −89.8 to 26.8; P = 0.37; absolute decrease 12.7% [95% CI, −34.5 to 9.0]). Central-blinded biopsy review found relative (absolute) decreases in rFSGS of 10.9% (3.9%), 17.0% (6.2%), and 20.5% (7.5%) at 3, 6, and 12 months posttransplant, respectively; these differences were not statistically significant. There was no difference in adverse events however a reduced rate of severe infections was noted in the bleselumab arm. No deaths occurred during the study.

Comment: Recurrent FSGS remains a challenging issue in kidney transplantation, with an incomplete understanding of its clinical-pathological mechanisms, a high recurrence rate post-transplant, and no specific treatment available. A bleselumab-containing regimen did not reduce the incidence of proteinuria (defined as a urine protein-creatinine ratio of at least 3 g/g) or achieve a statistically significant difference in biopsy-proven recurrence of FSGS. An open-label design, small sample size, insufficiently powered to show a prespecified difference between treatment arms are the study's major limitations. The lower rate of severe infections in the bleselumab arm may indicate that the bleselumab regimen was less immunosuppressive, however this observation should be examined in a larger, more comprehensive trials. Future studies should include a greater number of patients with data on residual kidney function, and the use of additional treatments (rituximab, plasma exchange, ACEi/ARBs) should be more precisely specified.

Dapagliflozin as a DEFENDER in critically ill patients: there is no data yet

Dapagliflozin for Critically Ill Patients With Acute Organ Dysfunction: The DEFENDER Randomized Clinical Trial

Tavares et al., 2024. JAMA. 2024;332(5):401-411.

Reviewed by Anastasiia Zykova

Summary: The DEFENDER was an open-label, multicenter study designed to evaluate the efficacy of adding an SGLT2 inhibitor, dapagliflozin (10mg), to standard of care versus standard of care alone in patients with acute organ failure. Among 507 ICU patients with at least one organ dysfunction, acute kidney injury (AKI) was diagnosed in 40.3% of patients in the experimental arm and 43.2% in the control arm, although most patients had a creatinine level of <1.5 mg/dl (<132,6 µmol/l) and AKI was the reason for ICU admission in 1.5% and 2.7% of patients, respectively. The most common reasons for ICU admission were infections and cardiovascular disease. The mean age in the groups was 63.3 years in the experimental arm and 65.4 years in the standard of care arm, with a male predominance in both. The primary outcome was a hierarchical composite of in-hospital mortality, initiation of kidney replacement therapy and ICU stay up to 28 days after randomization. Treatment with dapagliflozin did not result in a more favorable outcome, the hazard ratio was 1.01 (95%CI, 0.9 to 1.13, p=0.89). In the pre-specified subgroup analysis, there was no difference in patients with diabetes, cardiovascular disease and patients with different serum creatinine levels. Hospital mortality within 28 days was 35.5% in the dapagliflozin group compared to 34.4% in the standard of care group. The incidence of serious adverse events was similar between the two groups - 46.4% in the intervention arm and 47.5% in the standard of care arm; adverse events of special interest were rare and comparable between the two groups.

Comment: SGLT2 inhibitors have become a game-changer in the treatment of chronic diseases such as type 2 diabetes, chronic heart failure and chronic kidney disease, although their use in critical settings is still the subject of debate. In this study, adding an SGLT2 inhibitor to standard care was safe but did not improve clinical outcomes in critically ill patients with acute organ dysfunction. Limitations include a heterogenous cohort with a diverse spectrum of diseases, which may not benefit from flozins, i.e. sepsis. Further, the possible inadequate absorption of Dapagliflozin in this critically ill cohort is not accounted for. In addition, there were no data and no group stratification according to albuminuria, an important factor implying endothelial dysfunction that drives cardiovascular complications. Finally, the authors noted that while SGLT2 inhibition therapy in the DEFENDER trial could have most likely improved AKI, the study involved patients at low risk for this condition.

Spironolactone reduces aortic plague progression and left ventricular mass in patients with diabetes and CKD

Mineralocorticoid Receptor Antagonism Prevents Aortic Plaque Progression and Reduces Left Ventricular Mass and Fibrosis in Patients With Type 2 Diabetes and Chronic Kidney Disease: The MAGMA Trial

Rajagopalan et al., Circulation. 2024;150:663–676.

Reviewed by Anastasiia Zykova

Summary: The main objective of the study was to evaluate the effect of spironolactone on atherosclerosis and its surrogates in patients with type 2 diabetes with chronic kidney disease (CKD) and high cardiovascular risk. The primary endpoint was changes in thoracic aortic wall volume (TWV), a measure of composite wall thickness as absolute (ΔTWV) and partial values (ΔPWV), using 3T magnetic resonance imaging (MRI) at 12 months. There was a high drop-out rate due to the COVID19 pandemic, medication intolerance and difficulties in performing MRI. While 79 patients were randomized, 26 patients on spironolactone and 25 patients on placebo were analyzed at the end of follow-up. The mean age was 64 years, 46% were women and 50% were black. The groups were comparable with respect to cholesterol

levels (142.3±36.4 and 146.3±42.3), eGFR (48.4±16.3 and 46.1±17.3), HbA1c (7.29±1.1 and 7.3±1.4). At the 12-month, the ΔTWV was 0.037±1.9 cm^3 in the spironolactone group versus 1.2±1.7 cm^3 in the placebo group (P=0.022), representing an ΔPWV increase of 0.87±10.0% in the spironolactone group versus 7.1±10.7% in the placebo group (P=0.029). There was also a statistically significant decrease in left ventricular mass (LVM) in the spironolactone group comparing with the increasing in placebo. Plasma proteomic analysis of more than 7000 proteins revealed a different proteomic profile in the spironolactone group, with the most influence on aldosterone targets and collagen pathways, exhibiting anti-inflammatory and antifibrotic effects. The blood pressure changes were comparable between groups, hyperkalemia was more frequent in the intervention arm.

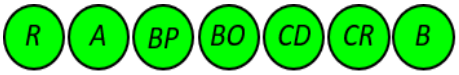
Comment: Mineralocorticoid receptor antagonists (MRAs) have reduced cardiovascular and kidney complications in patients with CKD, diabetes and albuminuria, but evidence regarding their effects on atherosclerosis progression is lacking. This study suggests that spironolactone may alter inflammation and fibrosis, potentially reversing endothelial dysfunction and reducing vascular stiffness independently of blood pressure. While the small sample size and unintentional unblinding due to potassium assessment are notable limitations, the proteomic analysis supports the MRI findings indicating that spironolactone can reduce atherosclerosis progression and LVM in patients with diabetes and CKD.

ISN Academy: Dialysis

POSIBIL: Clazakizumab's Promise in Reducing Inflammation for High-Risk Dialysis Patients

IL-6 inhibition with clazakizumab in patients receiving maintenance dialysis: a randomized phase 2b trial

Chertow et al., Nature Medicine, 2024, August; 30: 2328–2336.



Reviewed by Megan Borkum

Summary: The phase 2b dose-finding component of the POSIBIL6 trial aimed to assess the safety and efficacy of clazakizumab, an IL-6 inhibitor, in reducing inflammatory biomarkers among adult patients on maintenance dialysis. To be eligible, participants needed to have either cardiovascular disease or diabetes, have been on hemodialysis for at least 12 weeks, and have a hs-CRP level of ≧2 mg/L (i.e. exhibiting signs of inflammation). Patients were randomized in equal groups to receive clazakizumab in doses of 2.5 mg, 5 mg, or 10 mg, or a placebo via intravenous bolus every four weeks for up to six doses. The primary endpoint was the serum hs-CRP concentration's geometric mean ratio (GMR) at week 12. 127 patients were randomized, with 32 patients in each clazakizumab group and 31 receiving placebo. The cohort had a mean age of 62.4 years, with 33% female, 46% non-white, 71% with diabetes as the cause of kidney failure, and a median baseline hs-CRP of 8.3 mg/L. Results showed that clazakizumab reduced hs-CRP by week 12, with 86%, 90%, and 92% relative to placebo for the 2.5 mg, 5 mg, and 10 mg groups, respectively ($P < 0.0001$). None of the placebo patients achieved a hs-CRP <2 mg/L, whereas 79%, 82%, and 79% of the 2.5 mg, 5 mg, and 10 mg groups, respectively, reached this threshold. Further analysis of the secondary outcomes revealed improvements in downstream biomarkers of IL-6 activity and increased serum albumin. Safety data showed no cases of sustained grade 3 or 4 thrombocytopenia or neutropenia, and infections occurred at similar rates in the clazakizumab and placebo groups. There were six deaths across the trial, evenly distributed across all groups, with none attributed to clazakizumab.

Comment: This study explores the potential of clazakizumab to reduce inflammation in a high-risk population of patients with cardiovascular disease or diabetes on dialysis, where inflammation plays a critical role in poor outcomes. The promising results could pave the way for new therapeutic approaches to improve patient prognosis in this vulnerable group. Its strengths include a randomized design, multiple dosing groups, and a comprehensive efficacy and safety analysis. However, the small sample size, short duration, and limited long-term safety exploration limit the findings' generalizability. While no significant safety concerns were observed, further studies with larger populations and longer follow-ups are needed to confirm the long-term benefits and risks, particularly cardiovascular outcomes (the hypothesis to be evaluated in the phase 3 component of POSIBIL6).

Peritoneal Dialysis vs. Intermittent Hemodialysis: Which One is More Effective for Treating Acute Kidney Injury?

Lower-Dosage Acute Peritoneal Dialysis versus Acute Intermittent Hemodialysis in Acute Kidney Injury. A Randomized Controlled Trial

Parapiboon, W et al., Clin J Am Soc Nephrol. 2024 Aug 1;19(8):970-977.

Reviewed by Chiara Ruotolo

Summary: A multicenter, open-label, trial compare the efficacy of lower dosage peritoneal dialysis (PD) and intermittent hemodialysis (IHD) in the treatment of acute kidney injury (AKI). The study included patients with AKI diagnosis according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria who required kidney replacement therapy (KRT) under the conventional indications (metabolic acidosis, volume overload, hyperkalemia, and/or uremia) by nephrologist judgment. The exclusion criteria were contraindications for PD catheter insertion (anatomical reasons or peritonitis) or difficult vascular access for hemodialysis catheter insertion. Participants who had baseline eGFR <60 ml/min per 1.73 m2, life-threatening AKI complication (intractable hyperkalemia with serum potassium ≥7 mEq/L), severe metabolic acidosis (arterial blood pH ≤7.0), or volume overload with respiratory disturbance were excluded. The 157 included participants were randomly assigned to two groups: 80 patients in the PD group and 77 patients in the IHD group. The baseline characteristics (age, sex, body mass index, cause of AKI) were comparable between the two groups. Sepsis was the most common cause of AKI (68%). Most patients were in critical conditions (75% required inotropic drugs and 77% received respiratory support). The top three common indications for starting KRT were high blood urea nitrogen, oliguria, and refractory metabolic acidosis. IHD was performed 2-3 times per week, while PD was initiated immediately after bedside percutaneous catheter insertion (by a nephrologist) with varying glucose concentrations to enhance ultrafiltration. The primary outcome, 28-day mortality, was similar between the PD and IHD groups in both intention-to-treat (50% vs. 49%, risk difference 0.60, 95% CI -15.0 to 16.3) and per-protocol analyses (49% vs. 48%, risk difference 1.4, 95% CI -14.5 to 17.2). Secondary outcomes, including 28-day dialysis-free survival (42% vs. 37%, risk difference 4.6, 95% CI -11.1 to 20.3) and kidney recovery (39% vs. 26%, risk difference 12.7, 95% CI -2.8 to 28.2), showed no significant differences. Mean weekly Kt/Vurea was 2.11 in the PD group and 2.87 in the IHD group, with comparable metabolic control and net fluid balance after 7 days of dialysis.

Comment: This multicenter randomized controlled trial compared lower dosage acute PD with IHD, administered three times per week, in patients with AKI requiring KRT. The study found no significant difference in 28-day mortality between the two groups, though there was a trend toward higher kidney recovery in the PD group. Most PD patients achieved the target Kt/Vurea, while the IHD group fell short, yet mortality rates were comparable. Hypokalemia in the PD group highlighted the need for potassium supplementation. Peritonitis rates in PD were lower than in previous studies. The strengths of this study are that it is a multicenter randomized controlled trial that strictly followed the protocol; in addition, each center was either a tertiary hospital or had an affiliated medical school, with experience in the use of acute PD in patients with AKI. Limitations include the exclusion of patients with CKD, lack of data on pre-randomization fluid balance, and the use of IHD in patients with unstable hemodynamics, where continuous dialysis might have been more appropriate. While PD shows promise as a cost-effective option, further validation is needed.

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