ISN INTERNATIONAL SOCIETY OF NEPHROLOGY | RESEARCH ACT | CLINICAL TRIALS

Global Trials Focus

April 2021

The ISN-ACT (Advancing Clinical Trials) team presents this 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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Content

*ISN Academy: **Acute Kidney Injury***

In search of safe parameters for delayed initiation of RRT in AKI: how long is too long to wait?

Comparison of two delayed strategies for renal replacement therapy initiation for severe acute kidney injury (AKIKI 2): a multicentre, open label, randomised, controlled trial.

Gaudry et al, Lancet 2021, 397 (10281): p1293-1300 DOI 10.1016/S0140-6736(21)00350-0

R A BP BO CD CR B

Reviewed by Gallagher A

Summary: 278 adult intensive care patients on ventilation and/or inotropes with severe acute kidney injury, were monitored without renal replacement therapy (RRT) until they had ≥72 hours of oliguria or a blood urea nitrogen concentration (BUN) >112mg/dL. Participants were then randomised to receive immediate dialysis (labelled as 'delayed' strategy, relative to the onset of severe AKI) or had RRT postponed until a mandatory indication for dialysis occurred or BUN of 140mg/dL was reached ('more-delayed' strategy). With the delayed strategy, 98% received RRT while the more-delayed strategy, only 79% received RRT (p<0.0001). By day 28, there was no significant difference in the number of RRT-free days between the delayed strategy (12 days [IQR 0-25]) and the more-delayed strategy (10 days [IQR 0-24]; p=0.93). While 60-day mortality did not differ significantly between arms (44% of the delayed strategy group and 55% of the more-delayed strategy group died p=0.071), a pre-specified multivariable analysis

found a HR of 1.65 [95% CI 1.09-2.50, p=0.018] for 60-day mortality in the more-delayed group compared with the delayed group.

Comment This well-structured study looks to define how long is safe to delay RRT, potentially avoiding the need for dialysis in those who will spontaneously recover, while not leaving others vulnerable to complications of a prolonged uraemic state. Earlier trials have demonstrated that a delayed strategy to RRT is of benefit, but these have lacked clarity on how long RRT could be delayed. Gaudry and colleagues have added to the evidence base to define the upper limits of safe deferral of dialysis. The reasons for increased mortality with a more-delayed strategy need further evaluation, perhaps with consideration of the impacts of specific dialysis modalities.

ISN Academy: ***Genetic Kidney Diseases***

RNA interference therapeutic agent lumasiran reduces urinary and plasma levels of oxalate in children with primary hyperoxaluria type 1

Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1

Garrelfs et at. N Eng J Med 2021; 384(13):1216-1226. doi: 10.1056/NEJMoa2021712.

R A BP BO CD CR B

Reviewed by Bulanov N

Summary:

Primary hyperoxaluria type 1 (PH1) is a rare, progressive genetic disease caused by excessive hepatic production of oxalate, resulting in nephrocalcinosis and nephrolithiasis, kidney failure, and systemic oxalosis. The metabolic defect in PH1 results from a deficiency of the liver enzyme which converts the oxalate precursor glyoxylate to glycine. Lumasiran is a subcutaneously administered, liver-directed RNA interference therapy that reduces hepatic oxalate production and increases concentrations of glycolate, which can be excreted without difficulty. In this double-blind, phase 3 trial, 39 patients (6 years or older) with PH 1 were randomized in a 2:1 ratio to receive either lumasiran 3 mg/kg or placebo monthly for three doses, followed by maintenance doses every 3 months. Treatment with lumasiran resulted in reduced 24-hour urinary oxalate levels at 6 months compared to baseline (−65.4% in the lumasiran group versus −11.8% with placebo, 95% CI 62.3 to 44.8 percentage points of difference between treatment arms), improved numbers of patients with urinary oxalate ≤1.5 times the upper limit of normal (84% versus 0%, P<0.001) and reduced plasma oxalate levels (39.5 percentage points greater improvement from baseline for lumasiran compared to placebo, P<0.001). Injection site reactions occurred in 38% of patients receiving lumasiran compared to none with placebo, but there were no serious adverse events or deaths.

Comment

The study demonstrated that lumasiran is a highly effective treatment option for PH 1 patients. The drug quickly reduces urinary oxalate excretion, which is the cause of chronic kidney disease progression in PH 1. Treatment with lumasiran also substantially reduced plasma oxalate levels, which is expected to prevent or reduce systemic oxalosis. The limitation of the trial is the non-inclusion of patients younger than 6 years or with eGFR less than 30 ml/min/1.73 m^2. Larger scale studies are needed to confirm the promising safety profile and that the expected improvement in long-term clinical outcomes is realised.

ISN Academy: ***Anemia, Iron and Trace Elements***

Correction of iron status in non-anemic patients with chronic kidney disease: more questions than answers

A multicentre prospective double blinded randomised controlled trial of intravenous iron (ferric Derisomaltose (FDI)) in iron deficient but not anaemic patients with chronic kidney disease on functional status

Bhandari et al., BMC Nephrology (2021) 22:115 DOI:10.1186/s12882-021-02308-y

R A BP BO CD CR B

Reviewed by Zykova A

Summary: 54 patients with CKD 3b-5 and signs of iron deficiency without anemia were randomly assigned in a 1:1 ratio to receive a single dose of intravenous iron (ferric derisomaltose/iron isomaltoside) or placebo solution (0.9% NaCl). A double screen technique was used during infusions so that the patient participants would not see the brown (iron) or clear (saline) solutions being infused. The primary end-point was improved functional status according to a 6-min walk test (6MWT) at 1 and 3 months after the infusion, which showed no statistically significant difference between experimental and placebo arms at either time point (p = 0.736 and 0.741 respectively). There was no

statistically significant difference in hemoglobin level at 1 month (p = 0.195) and 3 months (p = 0.152). 95% of patients in the intervention arm achieved a serum ferritin >100microgram/L at 3 months compared to 21% in the placebo group (p < 0.001), and 67% achieved a transferrin saturation > 20 compared to 30% in the placebo group, respectively (p = 0.016). Results of quality of life assessment were the same in both arms.
Comment: The optimal management of iron deficiency in patients with CKD is still under debate, with many guidelines (including KDIGO, National Institute for Healthcare and Excellence, and the Renal Association) focusing on hemoglobin targets rather than iron parameters. The concept of physical improvement due to iron status correction is based on studies in non-anemic patients with heart failure, but this study has not demonstrated an improvement. According to the authors, the single-dose infusion was sufficient to improve the iron status, but the mean serum ferritin at 1 and 3 months were 266 and 233.4, respectively, which is still low by some iron management protocols. Trials with larger sample size or different iron dosing schedules may be required to further investigate this concept.

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*ISN Academy: **Haemodialysis***

Super High-Flux Haemodialysis, and High-Volume Postdilution Online Haemodiafiltration, Offer Similar Middle Molecule Clearance

Super high-flux hemodialysis provides comparable effectiveness with high-volume postdilution online hemodiafiltration in removing protein-bound and middle-molecule uremic toxins: A prospective cross-over randomized controlled trial
Thammathiwat et al. Ther Apher Dial 25:73-81

Reviewed by O'Hara DV

Summary: Super-high flux haemodialysis (SHF-HD, synonymous with high-cut off dialyzers) may have superior clearance rates to standard HD for uremic toxins, however it is expensive and not widely available. This study sought to determine whether similar clearance could be achieved using high-volume post-dilution online HDF (ol-HDF), with convective volume at least 23 litres/session, together with a new large pore size dialyser (PES 17D alpha). 13 HD patients underwent a 4-week lead-in period of high flux HD, then 12 weeks of treatment with either SHF or ol-HDF with the PES dialyser, then 4 weeks washout with high flux HD, then crossed over into the other treatment arm for 12 weeks. The two treatments resulted in similar reduction ratio values for the uremic toxin indoxyl sulfate and the middle-molecules beta-2-microglobulin and alpha-1 microglobulin, with mean a difference of 5.87 (95% CI -1.63, 13.37), 1.98 (95% CI,-0.21, 4.18), and 22.96 (95% CI, -1.91, 47.83), respectively. This reflects similar clearance within each session. The pre-dialysis levels of beta-2-microglobulin and alpha-1 microglobulin were reduced from baseline with SHF (from 50.01 ± 16.14 to 41.24 ± 9.78 mg/L, P < 0.005 and from 32.40 ± 9.76 to 24.58 ± 8.94 mg/dL, P < 0.05, respectively), but not with ol-HDF with the PES dialyser. Both treatments similarly improved the urea reduction ratio and spKt/V compared to baseline. SHF resulted in significantly greater albumin loss per session (4.2 ± 2.8 g vs 0.6 ± 0.8 g).
Comment:
While the two dialysis modalities offer similar within session clearance of indoxyl sulfate and middle molecules, SHF appeared to better reduce pre-dialysis levels of middle molecules, which may reflect overall superior clearance, but at the cost of significantly increased albumin loss. Both treatments require specialised equipment that is less available and more expensive than standard haemodialysis. Trials with larger sample sizes, and trials examining the effect of these therapies on long-term patient outcomes, are required.

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*ISN Academy: **Glomerular Diseases***

Rituximab vs Cyclophosphamide in Membranous Nephropathy: a call for a global non-inferiority trial

Rituximab or Cyclophosphamide in the Treatment of Membranous Nephropathy: The RI-CYCLO Randomized Trial
Scolari et al. J Am Soc Nephrol, Online ahead of print

Reviewed by Twining M and Franca Gois P

Summary: This was an open-label pilot randomised controlled trial comparing Rituximab (1g on days 1 and 15) with a cyclic corticosteroid-cyclophosphamide regimen (6-month cyclic regimen with corticosteroids alternated with cyclophosphamide every other month) in patients with membranous nephropathy and nephrotic-range proteinuria. Seventy-four participants were randomised and analysed by intention to treat. One patient discontinued treatment in the cyclic corticosteroid-cyclophosphamide group due to treatment intolerance, whereas 4 individuals

discontinued rituximab due to infusion-related reactions. In addition, one participant from the rituximab arm was switched to a non-study intervention (cyclosporine). The primary outcome was complete remission (i.e. proteinuria ≤0.3g/d). Six participants (16%) in the rituximab arm achieved complete remission at 12-months compared to 12 (32%) individuals in the cyclic-regimen arm (odds ratio 0.40; 95% CI: 0.13-1.23). Complete or partial remission (proteinuria at least 50% lower than baseline, and ≤3.5g/d) at 12 months was achieved in 23 participants (62%) receiving rituximab and 27 (73%) receiving the cyclic-regimen (OR, 0.61; 95% CI: 0.23-1.63). Patients in the cyclic corticosteroid-cyclophosphamide group presented more often with leukopenia (6 events per 100 patient years versus 0 with rituximab).

Comment: Given the cumulative toxicities of cyclophosphamide, safe and effective alternatives are sought. The authors showed similar outcomes in both rituximab and cyclic corticosteroid-cyclophosphamide. Low recruitment numbers (including withdrawal due to adverse events) result in a difficulty to draw conclusions in both the efficacy and adverse event rate of rituximab versus corticosteroid-cyclophosphamide therapy, therefore limiting ability to currently change clinical practice. The difficulty in recruiting patients with membranous nephropathy suggests that a global multicentre randomised trial is required. The authors also emphasise that a better understanding of factors predicting response to particular therapies are needed and might enable individualised treatment approaches.

Edited by Gallagher A, O'Hara DV and Smyth B