ISN Trial-List
September 2017

Once a month, the ISN-ACT (Advancing Clinical Trials) initiative team collects and publishes a list of important nephrology trials from the latest medical literature.

Hypertension

ISN Academy: Hypertension

Aspirin reduces the incidence of pre-term birth due to preeclampsia

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Rolnik, et al. N Eng J Med 2017;377(7):613-622

Preeclampsia is one of the leading causes of peripartum morbidity and preterm birth. While many trials and multiple meta-analyses have demonstrated the efficacy of aspirin in high-risk women, it is still unclear how 'high-risk' should be defined – meaning that many women may be missing the potential benefits of treatment. Rolnik, et al. utilised a risk calculator incorporating maternal characteristics and pregnancy history, serum biomarkers and uterine arterial flow patterns to identify women with a > 1% risk of preterm delivery (<37 weeks) due to preeclampsia. After screening over 26,000 women – of whom around 11% were considered high-risk by their algorithm – they were able to randomize 1776 women to aspirin 150mg daily or placebo from 11-14 weeks gestation (to continue until 36 weeks). Notably, over two-thirds of the cohort were nulliparous women and the prevalence of women with a history of preeclampsia, chronic hypertension or assisted fertilization was low. The primary outcome of delivery with preeclampsia before 37 weeks occurred in 1.6% of the aspirin group versus 4.3% in the placebo group (odds ratio 0.38; p=0.004). There were no significant differences in other secondary outcomes or adverse events. This important study demonstrates the utility of a comprehensive preeclampsia screening algorithm to accurately identify a cohort of women who benefit from this simple and inexpensive therapy.

Glomerular Diseases

ISN Academy: Glomerular Diseases

High dose oral corticosteroids may slow the progression of IgA nephropathy – but at a high cost.

Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial.

Lv, et al. *JAMA* 2017;318(5):432-442.

The use of systemic immunosuppression in IgA nephropathy has been an area of contention. The TESTING study follows in the wake of the STOP-IgA trial which showed an excess of infections and no change in long-term change in eGFR. TESTING differs from STOP-IgA in that the treatment group received only oral methylprednisolone (0.6-0.8mg/kg/day two months and weaned over 4-6 months) regardless of baseline eGFR (without the addition of cyclophosphamide in those with an eGFR <60ml/min/1.73m^2). The target recruitment was 750 participants, participants with IgA nephropathy, an eGFR >20mL/min/1.73m^2 and >1g/day proteinuria despite at least 3 months of renin-angiotensin system blockade. Recruitment was discontinued early due to an excess of severe adverse events in the treatment group. Among the 262 participants randomized (with a median follow up of 2.1 years), serious adverse events occurred in 14.7% of the treatment group compared with 3.2% in the control group. The majority of events in the treatment group were serious infections (including 2 deaths). The primary outcome (a composite of end-stage kidney disease, death due to kidney failure or a 40% decline in eGFR) was significantly reduced in the treatment group (5.9% vs 15.9%). Mean proteinuria and the mean rate of decline in eGFR was also lower in the treatment group (1.37g/day vs 2.36g/day and -1.79mL/min/1.73m^2 vs -6.95mL/min/1.73m^2). These challenging results highlight the need for novel immunotherapies that target the immune disorder driving IgA nephropathy without the risks of systemic immunosuppression.

Transplant

ISN Academy: Transplant

Low dose sirolimus and tacrolimus ER may be a feasible combination in low-risk renal transplant recipients

De novo low-dose sirolimus versus mycophenolate mofetil in combination with extended-release tacrolimus in kidney transplant recipients: a multicentre, open-label, randomized, controlled, non-inferiority trial.

Huh, et al. *Nephrol Dial Transplant* 2017;32:1415

The role of combined mTOR inhibitor and calcineurin inhibition in renal transplantation remains unclear. Huh, et al. hypothesised that that the combination of low-dose sirolimus and extended release (ER) tacrolimus might offer effective immunosuppression without the adverse effects frequently seen with standard dose mTOR inhibition. They randomized 158 living-donor or DBD renal transplant recipients to receive open-label sirolimus (target trough level 3-5ng/mL) or mycophenolate mofetil (MMF) 1-2g per day. Both groups received ER-tacrolimus (target trough 3-12ng/mL for one month, then 3-8ng/mL thereafter), corticosteroids and induction with basiliximab. Patients were followed for 12 months. Biopsy-proven acute rejection (BPAR) was diagnosed in four patients in the sirolimus group and 10 in the MMF group and the composite of BPAR, graft failure and death was also lower in the sirolimus group (6.6% vs 13.3%). Neither difference was statistically significant. There was no overall difference in adverse events although the incidence of wound complications was higher in the sirolimus group and the incidence of CMV and BK infection was lower (only the CMV difference reached statistical significance). Renal function was not different at 12 months. The authors concluded that low-dose sirolimus was non-inferior to MMF in combination with ER-tacrolimus. These results must be viewed in the context of relatively low doses of MMF in the control arm and a low number of endpoints. Nevertheless, this study demonstrates the feasibility of a novel immunosuppressive approach which may merit further study.

Peritoneal Dialysis

ISN Academy: Peritoneal Dialysis

Waiting two weeks to start peritoneal dialysis reduces leak after insertion of catheter

A Randomized Controlled Trial to Determine the Appropriate Time to Initiate Peritoneal Dialysis after Insertion of Catheter (Timely PD Study)

Ranganathan, et al. *Perit Dial Int. 2017;37:420-428*

The optimal waiting time from insertion of a tunnelled peritoneal dialysis catheter to starting peritoneal dialysis is not known. Ranganathan et al. set out to address this common clinical dilemma by randomizing 122 participants starting peritoneal dialysis for end-stage kidney disease to start dialysis at 1, 2 or 4 weeks after catheter insertion. They found rates of catheter leak were much higher in those randomized to start at 1 week compared to 2 or 4 weeks (28.2%, 9.5% and 2.4% respectively) – although only the difference between 1 and 4 weeks was statistically significant. These differences were confirmed in the per protocol analysis (32.4%, 10.5% and 3.3% respectively). In addition, they found that, among diabetic patients, the rate of technique failure was greater in those randomized to a week 4 start (28.6%) versus starting at week 1 or 2 (0% and 7.1%). Overall, although limited by a small sample size and relatively high rates of cross-over, this simple study may help clinicians to weigh the risks and benefits of delayed start to dialysis after catheter insertion.

Anaemia, Iron and Trace Elements

ISN Academy: Anaemia, Iron and Trace Elements

Oral HIF-prolyl hydroxylase inhibitors show promise in early phase anaemia trials

Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China

Chen, et al. Nephrol Dial Transplant. 2017;32(8):1373

Oral inhibitors of HIF-prolyl hydroxylase (HIF-PHIs) are a novel treatment for anaemia of chronic kidney disease that act by preventing the degradation of Hypoxia Inducible Factor (HIF). This leads to increased production of erythropoietin. Chen, et al. report the results of two Phase 2 trials of roxadustat conducted in Chinese maintenance dialysis and non-dialysis dependent chronic kidney disease participants. Both trials (containing 96 and 91 participants respectively) demonstrated the efficacy of roxadustat over a 6-8 week period. In addition, hepcidin levels were significantly reduced in those in the treatment arms and total iron binding capacity and transferrin levels were significantly increased. Total cholesterol also fell in the roxadustat arms. There were no significant differences in adverse events between the treatment or placebo groups. While these trials are encouraging, it remains unclear how these new agents compare to current treatments in terms of efficacy, safety and overall cost. Phase 3 trials are keenly anticipated.