

ISN-ACT Trial List

June 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.

Glomerulonephritis

Oral budesonide reduces proteinuria in IgA nephropathy

Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomised, placebo-controlled phase 2b trial

Fellström, et al. Lancet. 2017;389(10084):2117-2127

The mucosal immune system is linked to the pathogenesis of IgA nephropathy via the production of IgA from Peyer's patches within the intestine. Fellström, et al. conducted a novel randomized double-blinded trial of 'targeted-release' budesonide – designed to be released in the distal ileum – versus placebo in patients with IgA nephropathy and persistent proteinuria despite optimal angiotensin inhibition. One-hundred and fifty-three participants were randomized (1:1:1) to budesonide 16mg, budesonide 8mg or placebo. After 9 months follow up a 24.4% reduction from baseline proteinuria was observed in patients receiving budesonide. Moreover, while the placebo group saw an average 9.8% decline in eGFR from baseline, eGFR remained stable in the budesonide groups. No significant differences in adverse events were noted. This trial may herald a new approach to the treatment of IgA nephropathy. Longer term studies of patient-centred outcomes are eagerly awaited.

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(17\)30550-0/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30550-0/abstract)

Mycophenolate plus moderate-dose corticosteroids is equivalent to high-dose corticosteroids alone for IgA nephropathy with high-risk biopsy features but is associated with fewer adverse metabolic events

Mycophenolate Mofetil Combined With Prednisone Versus Full-Dose Prednisone in IgA Nephropathy With Active Proliferative Lesions: A Randomized Controlled Trial

Hou, et al. Am J Kidney Dis. 2017;69(6):788-795.

The optimal treatment of patients with IgA nephropathy and high-risk features on biopsy is not known. Hou, et al. randomized 176 patients with active proliferative lesions (cellular and fibrocellular crescents, endocapillary hypercellularity, or necrosis) and a diagnosis of IgA nephropathy to 6 months of mycophenolate mofetil (MMF) 1.5g/day plus prednisone (initial dose 0.4-0.6mg/kg/day) or prednisone (initial dose 0.8-1.0mg/kg/day). There was no difference in complete remission rates at 6 months (37% vs 38%) or 12 months (48% vs 53%). The number of participants experiencing at least one adverse event did not differ between groups although more patients in the prednisone only group developed new-onset diabetes and/or Cushing's syndrome. This study suggests that MMF may potentially have a role as a steroid sparing agent in the treatment of IgAN when immunosuppression is deemed necessary, but effects on clinical endpoints remain to be demonstrated. The lack of a placebo group also limits interpretation given uncertainty generated by recent trials of steroid based immunosuppression

[http://www.ajkd.org/article/S0272-6386\(17\)30008-2/abstract](http://www.ajkd.org/article/S0272-6386(17)30008-2/abstract)

Dialysis

Fewer episodes of intradialytic hypotension with HDF in older patients, but no impact on QOL or mortality.

Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly

Morena, et al. Kidney Int. 2017;91(6):1495-1509

Hemodiafiltration (HDF) is thought to reduce the risk of intradialytic hypotension but there is little evidence as to whether this translates to reduced patient intradialytic symptoms. Morena, et al. conducted the FRENCHIE trial to test the hypothesis that HDF reduces intradialytic symptoms compared with standard high-flux hemodialysis (HD) in a cohort of older (≥ 65 years) patients. They randomized 381 participants to HDF or HD in an open-label design and followed them for a median of 24 months. The primary outcome – the proportion of participants experiencing at least one adverse intradialytic event during month 2-6 of the study – did not differ between the two arms, although a per-protocol analysis showed fewer episodes of intradialytic hypotension and muscle cramps and an increase in arrhythmias in the HDF group. Pre-dialysis phosphate and $\beta 2$ -microglobulin were also reduced by HDF. There were no differences in quality of life or cardiovascular or all-cause mortality over the extended follow up period. This important trial suggests that any benefits of HDF in older dialysis patients may be modest.

[http://www.kidney-international.org/article/S0085-2538\(17\)30040-6/fulltext](http://www.kidney-international.org/article/S0085-2538(17)30040-6/fulltext)

HDF is not associated with reduced post-dialysis recovery time

A randomized, single-blind, crossover trial of recovery time in high-flux hemodialysis and hemodiafiltration

Smith, et al. Am J Kidney Dis. 2017;69(6):762-770

Recovery time after hemodialysis (HD) is emerging as an overlooked measure of dialysis tolerability and is now known to be linked to increased mortality. Smith, et al. designed a randomized crossover trial to determine if haemodiafiltration (HDF) improves recovery time compared with HD. One hundred patients, blinded to treatment allocation, were assigned to 8 weeks of HDF followed by 8 weeks of HD (or vice versa). Patient-reported recovery time did not differ between modalities (median: HDF 47.5min, HD 30min) although the proportion of patients reporting immediate recovery (0 mins) was significantly higher when receiving HDF (34.4% vs 32.2%). In contrast to Morena, et al. (see above) episodes of symptomatic intradialytic hypotension were significantly higher in the HDF group (8.0% vs 5.3%). This study confirms the feasibility of patient-reported recovery time as an outcome in clinical trials. However, it also highlights the ongoing uncertainty about the true benefits of HDF over HD.

[http://www.ajkd.org/article/S0272-6386\(16\)30635-7/abstract](http://www.ajkd.org/article/S0272-6386(16)30635-7/abstract)

Transplantation

Chlorthalidone is as effective as Amlodipine for hypertension in kidney transplant recipients

Chlorthalidone Versus Amlodipine for Hypertension in Kidney Transplant Recipients Treated With Tacrolimus: A Randomized Crossover Trial

Moes, et al. Am J Kidney Dis. 2017;69(6):796-804

Hypertension in renal transplant recipients is common and calcineurin inhibitors (CnI) are known to contribute. Recent work indicates that CnI activate the renal tubular sodium-chloride co-transporter suggesting that thiazide diuretics may have a role in the management of CnI-associated hypertension. Moes, et al. designed a randomized cross-over trial to test the hypothesis that chlorthalidone is non-inferior to amlodipine. They allocated 49 hypertensive transplant recipients taking tacrolimus to 8 weeks of chlorthalidone followed by 8 weeks of amlodipine (or vice versa). Among the 41 participants who completed the study there was no significant difference in

ambulatory systolic blood pressure at the end of each 8 week period. During treatment with chlorthalidone, significant reductions in proteinuria and edema were noted, as were increases in uric acid and HbA1c and a temporary reduction in eGFR. These results suggest similar short term anti-hypertensive efficacy for both drugs. However, the net effect of the thiazide-induced changes in metabolic and renal parameters remains unclear.

[http://www.ajkd.org/article/S0272-6386\(17\)30118-X/abstract](http://www.ajkd.org/article/S0272-6386(17)30118-X/abstract)

General Medicine

Combination of aerobic and resistance training better for obese older adults

Weight Loss, Exercise, or Both and Physical Function in Obese Older Adults

Villareal, et al. N Engl J Med. 2017;364(13):1218–1229

Enthusiasm for advising weight loss in obese older patients has been tempered by concern about worsening sarcopenia and physical function. Villareal, et al. hypothesized that a weight loss program incorporating resistance exercise would be superior to aerobic exercise or a combination of both in improving physical function. They randomized sedentary adults aged 65 years or older with a BMI of at least 30kg/m² and mild-moderate physical frailty to thrice weekly classes of aerobic exercise, resistance exercise or a combination of both (all accompanied by a structured weight loss program) or to a control group which received dietary advice alone. At the end of 6 months, weight loss was similar in all exercise groups and, in line with their hypothesis, lean body mass loss was least in the resistance group. Despite this, improvements in physical function (as assessed by gait speed, balance and strength) and SF-36 Physical Component Score were greatest in the combination group. This study suggests that combining resistance and aerobic exercise in older individuals attempting to lose weight results in better physical function than either type of exercise alone.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3114602/>
