

ISN Trial-List

February 2019



Once a month, the ISN-ACT (Advancing Clinical Trials) team collects and publishes a list of important nephrology trials from the latest medical literature. Each trial is reviewed in context and their risk of bias in seven key areas assessed.

Key to risk of bias assessment

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|----|------------------------------------|-----------------------------|
| R | Random sequence generation | High risk |
| A | Allocation concealment | Uncertain risk / not stated |
| BP | Blinding of participants/personnel | Low risk |
| BO | Blinding of outcome assessment | |
| CD | Complete outcome data | |
| CR | Complete outcome reporting | |
| B | No other sources of bias | |

ISN Academy: [Transplant](#)

Tacrolimus dosing in transplantation: one plus one equals one?

Once-daily vs twice-daily tacrolimus for de novo living kidney transplantation patients including ABO/HLA compatible and incompatible: A randomized trial

[Okumi, et al. Clin Transplant. 2018;32\(12\):e13423](#)

Although once-daily formulations of tacrolimus are widely available, the evidence supporting their equivalence is from trials that have included few patients with evidence of ABO or HLA incompatibility. In this pragmatic trial, Okumi, et al. randomized 125 de novo living kidney transplant recipients to once-daily or twice-daily tacrolimus in addition to basiliximab, mycophenolate mofetil and corticosteroids. Forty-nine (39.2%) of participants had ABO incompatibility or HLA incompatibility (in the form of donor specific antibodies) and received rituximab and plasmapheresis prior to transplantation. Rates of graft failure were similar in the once-daily and twice-daily groups at 5 years (6.5% vs. 9.5%, respectively; $P=0.009$ for non-inferiority at a risk difference margin of 10%). There were no differences at any timepoint in eGFR and no important differences in biopsy proven acute rejection, new onset diabetes, BK nephropathy or cytomegalovirus infection. This study provides confidence that once-daily tacrolimus is similar to twice-daily dosing in a population including recipients with pre-formed ABO or HLA antibodies. In doing so, it may assist in the uptake of once-daily dosing where favoured by other considerations such as patient preference and cost.



ISN Academy: [Glomerular Diseases](#)

Voclosporin may boost response rate in lupus nephritis, but questions remain

A randomized, controlled double-blind study comparing the efficacy and safety of dose-ranging voclosporin with placebo in achieving remission in patients with active lupus nephritis

[Rovin, et al. Kidney Int. 2019;95\(1\):219-231](#)

The role of calcineurin inhibitors in the management of lupus nephritis remains unclear. Rovin, et al. randomized 265 participants (from 79 sites and 20 countries) with active lupus nephritis to receive one of two doses of voclosporin (23.7mg or 39.5mg) or placebo in addition to mycophenolate and moderate-dose corticosteroids. At 48 weeks, complete remission (CR) was significantly more common in the low- and high-dose voclosporin groups compared to placebo (49.4%, 39.8% vs. 23.9%; OR 3.21 [95% CI 1.68, 6.13; $P<0.001$] and 2.10 [95% CI 1.09, 4.02; $P=0.026$], respectively). However, more participants experienced adverse events in the voclosporin groups compared to placebo (92.1% and 96.6% vs. 85.2%; low, high and placebo respectively) and an excess of deaths was noted in the low-dose group (10/89) as compared to high-dose (2/88) and placebo (1/88) groups. The limitations of this study included the use of a novel, low-dose rapid taper steroid regimen that may not be equivalent to usual standard of care. Also, 7 of the 13 deaths occurred at two sites in one country suggesting that the adverse safety signal might not be directly attributable to voclosporin. These results suggest that the addition of voclosporin to usual treatment of lupus nephritis may increase the chance of complete remission, however important concerns have been raised regarding the safety of this approach. Further studies are underway and their results are keenly anticipated.



Combination RAS blockade and reduced tacrolimus exposure associated with reduced IFTA

Comparison of the Effects of Standard Versus Low-dose Prolonged-release Tacrolimus with or without ACEi/ARB on the Histology and Function of Renal Allografts

[Cockfield, et al. Am J Transplant. 2018 Dec 23. doi: 10.1111/ajt.15225](#)

Gradual loss of renal allograft function with interstitial fibrosis/tubular atrophy (IFTA) on biopsy remains a key reason for shortened graft survival. The use of renin-angiotensin system (RAS) blockade and optimization of calcineurin inhibitor exposure may be beneficial. Cockfield, et al. aimed to test this hypothesis by randomizing participants receiving living or deceased donor kidneys without high-risk immunological characteristics in a 2x2 factorial design to low- or standard-dose prolonged release tacrolimus and to RAS blockade with angiotensin-converting enzyme inhibitor/angiotensin receptor blockers or to treatment of hypertension only if indicated and using other antihypertensives. The target trough level of tacrolimus in the standard-dose group was initially 12ng/ml until start of week 3, 10ng/ml to month 4 and 8ng/ml to month 6. The target in the low-dose group was 5ng/ml for the first 6 months. Thereafter dosing could be adjusted at the discretion of the treating physician. Among the 281 participants, 185 had biopsies available for assessment at 24 months. While there were no significant differences at 6 months, at 24 months the low-dose group had a lower IFTA prevalence than the standard-dose group (43.8% vs 71.6%; $P < 0.001$). There was no difference between the RAS blockade and non-RAS blockade groups. The lowest prevalence of IFTA was seen at 24 months in those assigned to the combination of low-dose tacrolimus and RAS blockade (37.0% vs. 48.8%, 73.7% and 69.4% in other groups). The risk of biopsy-proven acute rejection appeared greater in participants assigned to low-dose tacrolimus and non-RAS blockade antihypertensives (HR 2.48 [95% CI 1.13, 5.43; $P = 0.023$] vs. standard-dose/other antihypertensives and HR 2.69 [95% CI 1.22, 5.92; $P = 0.014$] vs. low-dose/RAS blockade). There were no differences in renal function between groups. Of note, the study was not blinded and diabetic nephropathy was a more common cause of primary renal disease in those allocated to standard-dose tacrolimus and as-needed non-RAS antihypertensive therapy. While this interesting study underlines the potential benefits of reduced tacrolimus exposure and use of RAS blockade in renal allograft recipients, it remains unclear if these changes actually result in improved renal function or graft survival.



ISN Academy: [Glomerular Diseases](#), [Pediatric Nephrology](#)

Levamisole and mycophenolate are comparable in frequently relapsing nephrotic syndrome

Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial

[Sinha, et al. Kidney Int. 2019;95\(1\):210-218](#)

Glucocorticoid therapy is typically an effective treatment for children with nephrotic syndrome, however a fraction of patients go on to have recurrent relapses are at risk of adverse outcomes - both from the disease process, and the treatment with glucocorticoids. Levamisole has been shown to be effective in reducing the rate of relapse (see [Triallist March 2018](#)), but has not been directly compared to mycophenolate (the other standard steroid sparing agent). This single-centre, open-label study randomised 207 participants between the ages of 6-18 years with frequent relapsing, or steroid-dependent, nephrotic syndrome to receive mycophenolate mofetil (MMF) or levamisole over a 12-month period, with a median follow-up of 43-months. Although there was a dramatic reduction in relapse rates in both groups, there was no significant difference in the rate of relapse between the MMF and levamisole groups (mean difference in incident rate ratio -0.29 [95% CI -0.65, -0.08; $P = 0.12$]). Forty-one percent of patients receiving MMF and 34% of patients receiving levamisole reached a sustained remission ($P = 0.20$) following discontinuation of prednisolone, with only 14.5%, and 16.4% having frequent relapses, respectively ($P = 0.75$). Therapy with MMF was not superior to levamisole with similar treatment failure rates (15.8% vs. 20.6%). At the end of the follow-up period, the number of participants with sustained remission (27.1% vs. 19.4%), infrequent relapses (57.1% vs. 53.7%), frequent relapses (14.3% vs. 25.4%), and late steroid resistance (1.5% vs. 1.4%) were similar between the groups ($P > 0.05$). While this small study was not blinded and the wide confidence intervals do not exclude an important difference between the two treatments, it still provides useful guidance on steroid-sparing regimens in children with relapsing nephrotic syndrome while waiting for greater clarity from further multi-centre studies.



Calcium carbonate associated with greater coronary calcification compared to activated charcoal and lanthanum carbonate

Effects of oral activated charcoal on hyperphosphatemia and vascular calcification in Chinese patients with stage 3-4 chronic kidney disease

[Gao, et al. J Nephrol. 2018 Dec 26. doi: 10.1007/s40620-018-00571-1](#)

There has been little study of the effect of activated charcoal on hyperphosphatemia (an important risk factor for vascular calcification) in those with CKD. Gao, et al. initially randomised 97 participants with CKD Stage 3 or 4 to receive either oral activated charcoal (OAC), or placebo until they developed hyperphosphatemia. Participants were then randomly divided into 3 groups to receive OAC, calcium carbonate (CC), or lanthanum carbonate (LC). Coronary CT scans were performed prior to starting phase 2 and then every 6 months to evaluate vascular calcification. At the end of the first phase, there were significantly fewer patients in the OAC group that progressed to have hyperphosphatemia (28.6% vs. 79.2%, $P < 0.001$). At the end of the second phase there were significant differences in coronary calcification scores between the OAC, CC, and LC groups (443 vs. 543 vs. 357, $P < 0.01$), with the OAC and LC groups were superior to the CC group ($P < 0.01$), without a significant difference between the OAC and LC groups. There was a trend to more adverse events in the OAC group, with 7 patients encountering mild-moderate side effects compared to the 3 patients in the CC group, and 2 patients in the LC group. These results suggest that OAC may minimise hyperphosphatemia and coronary calcification (at least compared to placebo or CC). However, the conclusions are limited owing to it being a single-centre study with few participants and a methodology that does not adequately account for the impact of a participant experience in phase 1 on their results in phase 2.



Can targeting a higher hemoglobin preserve renal function following transplant?

The effect of maintaining high hemoglobin levels on long-term kidney function in kidney transplant recipients: a randomized controlled trial

[Tsujiata, et al. Nephrol Dial Transplant. 2018 Dec 17. doi: 10.1093/ndt/gfy365](#)

Post-renal transplant anemia is a common phenomenon and associated with decline in allograft function nephropathy in transplant patients. Meta-analyses do not suggest a role for ESAs in preserving renal function in those with chronic kidney disease (CKD), although the evidence in the renal transplant population is limited. This unblinded study by Tsujiata, et al. randomised 127 participants with anemia following renal transplantation to a target hemoglobin of 125-135 g/dl vs. 105-115g/dl using supplemental iron and ESAs and followed them over a 3-year period. Participants allocated to the high-hemoglobin group had a mean hemoglobin level of 128 ± 0.7 g/l vs. 115 ± 1.2 g/l in the low-hemoglobin group, with mean ESA dose being higher throughout the study. There was a significantly greater decline in eGFR in the low-hemoglobin group over the duration of the study (-5.1 ± 9.5 ml/min/1.73m²) than in the high-hemoglobin group (-1.0 ± 8.4 ml/min/1.73m²) ($P = 0.02$). Adverse events were similar. This trial adds to the debate surrounding higher hemoglobin targets in renal transplantation, but is limited by being only two centres and it was not powered to adequately assess safety. Larger multi-centre trials are needed before employing new hemoglobin targets in renal transplant recipients.

