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ISN Academy: Glomerular Diseases

Belimumab in addition to mycophenolate or cyclophosphamide-based therapy is effective and safe in the treatment of active lupus nephritis

Two-year, randomized, controlled trial of belimumab in lupus nephritis

Furie et al, NEJM 2020;383(12):1117-28

Reviewed by Chung E

About the study: Four hundred and forty eight adults with biopsy-proven lupus nephritis class III, IV or V (active or active and chronic lesions), urine protein:creatinine ratio (uPCR) ≥1 g/g and an eGFR >30 ml/min/1.73m² (baseline 100.5 ± 40.2) were randomised to belimumab IV 10mg/kg (D1, 15, 29, 43, 57, 71, 85, 99).

Results: The belimumab arm experienced a higher renal response compared to placebo at week 104 (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.0 to 2.3) and week 54 (OR 1.6, 95% CI 1.1 to 2.4), driven by reduction in proteinuria and no need for rescue therapy.
and every 28 days afterwards until week 100) or placebo, in addition to standard therapy (mycophenolate mofetil or cyclophosphamide/azathioprine, and prednisolone). Renal response at week 104 was defined as uPCR ≤0.7, eGFR <20% reduction from baseline or >60ml/min/1.73m², and no need for rescue therapy. The major secondary endpoint was a complete renal response at week 104 defined as uPCR <0.5, eGFR <10% reduction from baseline or ≥90ml/min/1.73m², and no need for rescue therapy.

Treatment with belimumab was also associated with a higher complete renal response at week 104 compared to placebo (OR 1.7, 95% CI 1.1 to 2.7). End-stage kidney disease and doubling of serum creatinine were rare in each group. There were no differences in adverse events.

**Comment:** This study found that belimumab in addition to standard treatment was more effective than standard treatment alone in inducing clinical remission of active class III-V lupus nephritis, without an increased risk of harm over 2 years. The renal response was driven by reduction in proteinuria and the study population had preserved kidney function. The positive result was driven by benefit in those patients treated with mycophenolate with no sign of benefit in those who received cyclophosphamide, a finding may warrant exploration in future studies. We await any recommendations from the KDIGO 2020 Clinical Practice Guideline on Glomerular Diseases on multi-targeted therapy in active lupus nephritis.

**Two drugs are better than one: support for combination therapy to reduce proteinuria in comorbid diabetes and hypertension**

A Prospective Single-Blind Randomized Trial of Ramipril, Eplerenone and Their Combination in Type 2 Diabetic Nephropathy

El Mokadem et al. Cardiorenal Med. Published online ahead of print. DOI: 10.1159/000508670

Reviewed by Gallagher A

**About the study:** Seventy five participants with stage one hypertension, microalbuminuria and diabetes were randomised to ramipril 10mg, eplerenone 50mg or a combination of the two in a 1:1:1, single-blinded fashion. Maximum doses were achieved over a month and then follow up continued for 24 weeks. The primary endpoint was the % change in urine albumin:creatinine ratio (uACR) at the end of the 24th week compared to baseline. Secondary endpoints included changes in BP, eGFR and serum potassium.

**Results:** Ramipril and Eplerenone monotherapy reduced microalbuminuria to a similar degree (P=0.95) whereas combination therapy had comparatively greater reductions vs both single agents (P=0.0001) [multivariate analysis of % change in uACR Epl/Rami vs. Ramipril -23.65 (95% CI -136.65 to -10.65) P= 0.001]. BP decreased across all three treatment arms, most significantly with dual therapy. There was a positive correlation between % reduction in SBP and % reduction of uACR. There were similar rates of sustained hyperkalaemia across the three groups, however more cases with eGFRs <60ml/min/1.73m². Of note, individuals were excluded from analysis if hyperkalaemia or hypotension occurred (similar incidence in three treatment arms).

**Comment:** This small trial affirms the findings of previous studies that good blood pressure control and ACEI/MRA combination therapy is an effective tool to reduce microalbuminuria in individuals with diabetes. As proteinuria is a known potent risk factor for progression of diabetic kidney disease and cardiovascular, this paper addresses a clinically important treatment target. Of note, this study included ACEI and eplerenone naïve participants with mild hypertension and microalbuminuria only. As a result it is important to consider the generalisability of these results to more complex diabetes and more advanced stages of hypertension. Further studies with long term follow up and inclusion of eGFR decline
and CKD progression would help support the long term renal benefits of this intervention on diabetic kidney disease.

**SGLT-2 inhibition strikes again**

Dapagliflozin in Patients with Chronic Kidney Disease  

Reviewed by Chou A

**About the study:** 4304 participants with eGFR 25-75ml/min/1.73m² and urine ACR of 200-5000mg/g randomised to dapagliflozin 10mg daily vs. placebo in a multicentre international trial. These individuals included those with and without diabetes. All patients were required to be receiving a stable dose of an ACE-inhibitor or ARB for ≥ 4 weeks prior to commencement.

**Results:** Over a median of 2 years, a primary outcome event (decline of eGFR ≥50%, onset of ESKD or death from renal or cardiovascular cause) occurred in 197/2152 (9.2%) in the dapagliflozin group vs. 312/2152 (14.5%) of placebo group (HR 0.61; 95% CI 0.51-0.72, p<0.001). NNT = 19.

**Comment:** This was a well-designed randomised controlled trial that was stopped early because of demonstration of efficacy. Its strengths include the large patient numbers, inclusion of a balanced number of diabetics and non-diabetics and demonstration of strong internal and external validity. Dapagliflozin was found to be superior in reducing the composite risk of sustained eGFR decline, progression to ESKD and death from renal or cardiovascular causes, even in the absence of diabetes, suggesting a potential broader application of this drug to reduce the progression of CKD and its complications.

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**Chewing gum may improve dry mouth symptoms in hemodialysis patients**

The effect of chewing gum on dry mouth, interdialytic weight gain, and intradialytic symptoms: A prospective, randomized controlled trial  
Ozen et al. Hemodial int. Online before print

Reviewed by O’Hara D

**About the study:** Forty four participants on chronic hemodialysis experiencing dry mouth symptoms (xerostomia) were randomised to either chew gum of their own choosing for 10 minutes 6 times per day, as well as when feeling dry in the mouth or thirsty, or to not chew gum. Participants were followed for 3 months with testing of 3 saliva samples over the course of the trial, and symptom assessment with the Visual Analogue Scale (VAS).

**Results:** The study demonstrated statistically significant reductions in xerostomia severity VAS scores with chewing gum (P < 0.001), and statistically significant improvements in the salivary flow rate (P < 0.001) compared to control, although point estimates for mean differences were not provided. There was no change in interdialytic weight gain.

**Comment:** This study is the first randomised trial of chewing gum for xerostomia in hemodialysis. While further trials with larger sample size may be needed to convincingly demonstrate a benefit, the intervention is well tolerated, relatively inexpensive and appears to produce a symptom benefit, and could therefore be considered when managing this common symptom.
**Aldosterone blockade slows CKD progression**

The effect of aldosterone and aldosterone blockade on the progression of chronic kidney disease: a randomised placebo-controlled clinical trial.


Reviewed by Shah N

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**About the study:** Forty eight participants with chronic kidney disease and elevated aldosterone levels (>15.0 ng/dL) were randomised to receive 25mg eplerenone vs. placebo. The study follow-up was 36-months. The primary outcomes were HOMA-IR (a measure of insulin resistance), rate of eGFR change, incidence of CVD, and mortality.

**Results:** During the study period, eplerenone at a 25mg/day dose had no effect on systolic blood pressure, diastolic blood pressure, or proteinuria when compared to placebo. The eGFR levels were significantly higher in the eplerenone group compared to placebo at 24-months (64.67±3.76 vs. 55.99±3.74 ml/min/1.73 m², p <0.05) and 36-months (61.86±3.50 vs. 54.62±3.67 ml/min/1.73 m², p < 0.05).

**Comment:** This two-stage study used prospective, observational data to identify the quintile range of plasma aldosterone associated with the most significant eGFR decline over a 3-year period. Using a threshold of >15.0mg/dL, participants were randomised to eplerenone or placebo. This small study suggests a renoprotective effect of aldosterone blockade independent of the effects on blood pressure and proteinuria. Coupled with the recently reported FIDELIO-DKD study, these results further support the notion that aldosterone antagonism slows the progression of chronic kidney disease.

**Finerenone may slow progression of diabetic kidney disease**

Effects of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes (FIDELIO-DKD)

Bakris et al. N Engl J Med. (Online before print) DOI: 10.1056/NEJMoA2025845

Reviewed by Kim D

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**About the study:** 5734 participants with CKD (eGFR 25-75ml/min/1.73m²), albuminuria and type 2 diabetes on maximum tolerated ACEI/ARB across 48 countries were randomised to finerenone (n=2833), a nonsteroidal, selective mineralocorticoid receptor antagonist versus placebo.

**Results:** The incidence of the primary composite outcome (kidney failure, sustained decreased of > 40% in eGFR, death from renal cause) was significantly lower in the finerenone group (17.8%) compared to placebo (21.1%) (p = 0.001) after 3 years. Cardiovascular and stroke events were also lower with finerenone (13%) compared to placebo (14.8%) (p=0.03). Finerenone had a 31% greater reduction in urine albumin-to-creatinine ratio (95% CI 0.66 to 0.71). The number of adverse events were similar (31.9% v 34.3%), however hyperkalaemia was more common with finerenone (18.3%) compared to placebo (9%). At trial conclusion, 822 patients (29%) of the finerenone group and 801 placebo patients (28.2%) had discontinued therapy.

**Comment:** There is ongoing research surrounding various pharmacological measures to slow down the progression of proteinuric CKD and DKD. This trial has demonstrated that finerenone, in conjunction with maximum RAAS blockade, has modest renoprotective and cardioprotective effects. This is proposed to be mediated through anti-inflammatory, antifibrotic and natriuretic mechanisms. There were equally high discontinuation and adverse event rates amongst both groups, however double the incidence of hyperkalaemia with finerenone which may limit its use in clinical practice. Further safety data and insight into long term outcomes are required, which may be addressed in the future by the FIGARO-DKD trial.
**Effect of higher dialysate magnesium on arterial stiffness and blood pressure**

Consequences of Supraphysiological Dialysate Magnesium on Arterial Stiffness, Hemodynamic Profile, and Endothelial Function in Hemodialysis: A Randomized Crossover Study Followed by a Non-Controlled Follow-Up Phase

Del Giorno et al. Adv Ther. 2020;37:4848–4865

Reviewed by Smyth BJ

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<th>About the study:</th>
<th>Thirty-nine individuals on dialysis were randomized to receive two weeks of standard (0.5mmol/l) or high (0.75mmol/l) dialysate magnesium (DMg) in a cross-over design.</th>
<th>Results: At the end of two weeks of treatment with higher DMg brachial pulse wave velocity (a measure of arterial stiffness) was improved (mean difference -0.91m/s, 95% CI -1.52 to -0.29; P=0.014) and systolic blood pressure was lower (mean difference -12.96, 95% CI -24.71 to -1.22; P=0.032). No carry-over effect or adverse events were noted.</th>
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**Comment:** This study found a substantial difference in blood pressure and in a marker of arterial stiffness. These effects could have an important impact on cardiovascular health in dialysis patients. However, this study is small and the short time spent on each of the DMg concentrations (only 6 dialysis sessions) means one cannot be confident that such differences would be sustained over the medium term (let alone whether they would affect cardiovascular pathology). Moreover, none of the other small randomized trials of higher DMg levels published in the last two years reported such a large decrease in systolic blood pressure. Nevertheless, this study reflects growing interest in higher DMg as a means of improving vascular calcification and cardiovascular pathology in dialysis patients.

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**Leave those bugs alone! Support for antimicrobial stewardship in asymptomatic bacteriuria post-transplantation**

Antibiotics versus no therapy in kidney transplant recipients with asymptomatic bacteriuria (BiRT): a pragmatic, multicentre, randomized, controlled trial

Coussement et al. Clinical Microbiology and Infection. Online ahead of print

Reviewed by Gallagher A

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<th>About the study:</th>
<th>One hundred and ninety-nine kidney transplant recipients ≥2 months post transplantation with asymptomatic bacteriuria were randomised to antibiotics or no therapy. This was a multicentre, parallel-group, open-label trial.</th>
<th>Results: The primary outcome was incidence of symptomatic UTI during the 1-year follow-up. Overall, 29.1% participants developed at least one symptomatic UTI in the 12 month follow-up period. The risk of symptomatic UTI did not differ significantly with 27% in the no antibiotic group and 31% in the antibiotic group progressing to symptomatic UTIs (HR 0.83, 95%CI: 0.50-1.40, p=0.49). Antibiotics had no significant impact on any secondary clinical outcomes including eGFR, rejection and incidence of pyelonephritis. Participants receiving antibiotics had fewer episodes of asymptomatic bacteriuria but at the expense of more days on antibiotics and more resistant strains of bacteria in subsequent cultures.</th>
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**Comment:** This well designed trial supports antimicrobial stewardship to prevent bacterial resistance in a population high risk for infection. While it was an open label study, assessors were blinded to treatment allocation to ensure unbiased reporting of outcome measures. They found no clinically significant risk of permitting continuation of asymptomatic bacteriuria, supporting a less is more approach.
approach in monitoring individuals post renal transplantation. It is important to note that this study was performed in a European cohort and had few participants less than six months since transplantation before generalising their findings to patients transplant in other regions in the early phases post-transplant, respectively.