Cemdisiran for complement-mediated inflammation in IgA nephropathy: A new therapy?

Phase 2 Trial of Cemdisiran in Adult Patients with IgA Nephropathy: A Randomized Controlled Trial

Reviewed Megan Borkum

Summary: Cemdisiran is a small interfering RNA molecule that blocks terminal complement pathway activation and consequent inflammation and tissue injury by suppressing C5 production in the liver. This phase 2, 36-week, double-blind study compared cemdisiran (600mg administered subcutaneously every 4 weeks) to placebo in biopsy-proven primary IgA nephropathy (IgAN). 31 adult participants on a stable dose of renin-angiotensin system inhibitor therapy (ACEi or ARB for >3 months), with no recent steroids or other immunosuppression, an eGFR ≥30ml/min/1.73m² and proteinuria ≥1 g/day, were randomized in a 2:1 ratio (cemdisiran, n= 22 vs placebo, n = 9). Both arms (cemdisiran vs placebo) were similar in terms of baseline demographics and disease characteristics, including comparable mean age (41 vs 38 years), median eGFR (68 vs. 47ml/min/1.73m²), mean 24-hour urinary protein to creatinine ratio (UPCR) (2.0 vs. 1.6g/g) and MEST-C score. Most patients were male and Asian. Blood pressure was well controlled between the treatment groups. At the end of week 32, the primary endpoint of the change from baseline in 24-hour UPCR in cemdisiran-treated participants compared with placebo was a mean reduction of 37.4% (90% CI: –61.0, 0.5). The change from baseline to week 32 in 24-hour urine total protein, a secondary endpoint, was a mean reduction of 36.2% (90% CI: –61.6, 6.0). Further, 22.7% of those treated with cemdisiran (vs 0% with placebo) achieved ≥50% reduction in 24-hour urine protein at week 32. Spot urine data were also consistent with 24-hour UPCR data, which showed an initial treatment effect emerging at week 8 that was sustained over time. This preceded a reduction in serum C5 level that started at week 4 (which suggests a reduction in the glomerular complement activation). The drug had an acceptable safety profile, including a lack of infections with encapsulated organisms. Adverse events in the cemdisiran arm included injection-site reactions (41% vs 22% in placebo), which were mostly mild and transient, and mild non-therapy-related peripheral edema (14% vs 11% in placebo). No adverse events led to treatment or study discontinuation.

Comment: IgAN remains the most common cause of primary glomerular disease worldwide. New developments in the understanding of the pathogenesis of IgAN have resulted in multiple clinical trials targeting disease-specific pathways to prevent kidney failure while minimising systemic side effects of therapies. This multi-pronged treatment approach includes reducing pathogenic IgA production, mitigating the consequences of ongoing nephron loss, timely
reduction of glomerular inflammation and stopping pro-fibrotic signals. No single drug can achieve all these goals; however, the available therapeutic strategies are rapidly evolving. These promising data support further evaluation of cemdisiran as a potential complement pathway inhibitor reducing inflammation in IgAN. However, limitations of this study include the small number of participants and short treatment duration, which should be considered when interpreting safety data and efficacy endpoints. It is unclear if a phase III study of cemdisiran in IgAN is planned.

**Should you PROCEED with surgery or tablets in peritoneal dialysis patients with advanced secondary hyperparathyroidism?**

**Impact of Parathyroidectomy Versus Oral Cinacalcet on Bone Mineral Density in Patients on Peritoneal Dialysis With Advanced Secondary Hyperparathyroidism: The PROCEED Pilot Randomized Trial**

**Wang et al., Am J Kidney Dis, 2024 Apr;83(4):456-466.e1.**

Reviewed by Ahad Qayyum

**Summary:** This head-to-head open-label pilot recruited 65 peritoneal dialysis (PD) participants with advanced secondary hyperparathyroidism (2HPT) to evaluate whether medical therapy (oral cinacalcet, n = 33) or surgery (total parathyroidectomy with forearm autografting, n = 32) was superior in improving bone mineral density (BMD). Advanced 2HPT was defined as an intact PTH level >= 800 pg/ml despite maximal vitamin D analogue treatment or a serum calcium >= 2.5mmol/L with radiological evidence of parathyroid hyperplasia/nodularity (without the use of vitamin D analogues). An initial daily dose of 25 mg of oral cinacalcet was prescribed. The dosage could be increased by 25 mg every 12 weeks up to a maximum tolerated dose of 100 mg per day to maintain intact PTH levels within 2 to 9 times the upper reference limit of the laboratory. Both groups (oral cinacalcet vs surgery) were similar in age (57 vs 56), proportion of males (14/33 vs 12/32) and duration of PD (62 vs 60 months). The participants were followed up for a period of 12 months, during which they had a DEXA scan on day 0 and then at 12 months. A large proportion of the participants in both groups were found to have low BMD at baseline, with osteopenia/osteoporosis most prevalent at the distal radius. At the end of the 12-month study period, both the cinacalcet-treated group and the total parathyroidectomy group had significantly improved BMD of the lumbar spine and femoral neck, but the improvement was greater with total parathyroidectomy (P<0.001). There were also significant improvements in T- and Z-scores in both groups (oral cinacalcet vs surgery) over 12 months in the lumbar spine (change in T-score over 12 months: 0.30 vs 1.00; change in Z-score over 12 months: 0.40 vs 0.90), and of the neck of femur (change in T-score over 12 months: 0.10 vs 0.70; change in Z-score over 12 months: 0.20 vs 0.70). There was no significant change in BMD, T- or Z-score in the distal radius with either intervention.

**Comment:** This study demonstrates a high prevalence of low BMD and osteopenia/osteoporosis in PD patients with advanced 2HPT. BMD of lumbar spine and neck of femur improves both with oral cinacalcet and total parathyroidectomy, but the latter was found to result in greater improvement in BMD. The bone density of the distal radius did not improve in either group. As a rationale for this observation, the authors suggest differing effects of therapy on cortical (distal radius) vs trabecular bone and possibly the short follow-up duration. The study's main limitations are the small sample size, limited follow-up period of 12 months, and lack of bone biopsies to assess bone turnover, volume and mineralization.

**A simple method to reduce hypotension during hemodialysis: ascending-descending ultrafiltration with linear sodium profiling**

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**ISN Academy: Dialysis**
The effect of ascending-descending ultrafiltration and sodium profiles on blood pressure in hemodialysis patients: a randomized cross-over study


Reviewed by Dominik Tuechler

Summary: This single-centre study used a cross-over design to assess the influence of ascending-descending ultrafiltration (A/D-UF) and sodium profiles on the blood pressure of 20 participants experiencing hypotension during haemodialysis (HD). Each patient had 16 HD sessions with the intervention protocol or routine HD with 4 wash-out HD sessions between switching to the other treatment. In both treatments, hourly blood pressure (BP) measurements were taken, with the last one taken after HD. The intervention protocol involved 3 ultrafiltration (UF) phases and a linear sodium profile. The UF phases were divided into an ascending phase, taking 25.5% of the patient’s total weight with low UF; an aggressive phase, taking 51.2% of the patient’s total weight at maximum UF, and a descending phase, taking 23.6% of the patient’s total weight with low UF. The sodium concentration of the dialysate started at 150mmol/L and decreased linearly to 138mmol/L by the end of the HD. In routine HD, UF and sodium concentration (140 mmol/l) were stable during the HD session. This study consisted mostly of men (60%), with a mean age of 58 years and a mean HD duration of 54 months. Most had a fistula (70%) and were receiving high-flux HD (85%). There was no significant difference in systolic or diastolic BP before, during or after HD with A/D-UF profiling (P>0.05). In contrast, there was a significant difference (P<0.05) for both parameters during routine HD, with a drop of nearly 20mmHg in systolic BP by the end of dialysis. The difference in mean arterial pressure (MAP) was also significant (p < 0.05) in both groups, but the MAP increased in the intervention group whilst it decreased in the routine HD group by the end of the session. There was also a significant reduction in symptomatic intradialytic hypotension with the application of A/D-UF (15% vs 55%; P=0.002).

Comment: Hypotensive episodes during HD are a major burden of morbidity and mortality for these patients. Despite this, only a few studies have assessed the effect of UF profiling, dialysis temperature, and sodium profiling on BP during HD. This study proposes a simple and cost-effective method to reduce hypotensive episodes in HD by modifying the UF profile in an ascending-descending fashion with linear sodium concentration. However, the study has major limitations due to the small sample size (n=20), single centre design, homogeneity in dialysis modalities (85% high flux HD), and missing baseline characteristics such as comorbidities and ethnicity. Further, due to the unblinded interventional procedure, selection and positive bias during the measurements cannot be ruled out. Overall, A/D UF with linear sodium profiling may be a valid alternative option for HD patients suffering from hypotension during the treatment. However, given this is a small study, more robust large-scale research in a double-blinded way are needed to test this hypothesis.

Proliferative Lupus Nephritis and therapy with Voclosporin

Efficacy of Voclosporin in Proliferative Lupus Nephritis with High Levels of Proteinuria


Reviewed by Maria Chiara Pelle

Summary: The AURORA 1 trial is a phase 3, placebo-controlled, double-blind study that evaluated the efficacy of oral voclosporin (23.7 mg twice daily) versus placebo in adults with active lupus nephritis, in addition to therapy with mycophenolate mofetil (MMF, target dose 2g/day) and low-dose glucocorticoids. In this post hoc analysis, 148 participants with class III or IV lupus nephritis and high levels of baseline proteinuria (urine protein–creatinine ratio (UPCR) over 3 g/g) were evaluated. Most of the participants had a histopathologic diagnosis of class IV lupus nephritis with or without class V lesions. Both groups had a mean age of 31 years, with female predominance and were race and ethnicity diverse. Mean baseline UPCR levels (voclosporin, 6.2 g/g vs. 5.7 g/g, placebo) and the average duration since lupus nephritis diagnosis (3 years voclosporin vs. 3.3 years, placebo) were comparable. At 12 months, 34% (26/76) of voclosporin-treated participants compared with 11% (8/72) in the placebo arm had achieved...
a complete kidney response, defined as a composite end-point of UPCR ≤ 0.5 g/g with stable eGFR, use of low-dose glucocorticoids, and no use of rescue medication (odds ratio, 4.43; 95% confidence interval [CI], 1.78 to >9.99; P=0.001). Similarly, there was a significantly higher percentage of partial kidney response (≥50% reduction from baseline UPCR) in the voclosporin arm compared to the placebo (odds ratio, 1.60; 95% CI, 0.8 to 3.20; P=0.18). Moreover, the median time to UPCR ≤ 0.5 g/g was earlier in voclosporin-treated participants (hazard ratio, 2.07; 95% CI, 1.19 to 3.60; P=0.01). Voclosporin was well tolerated, with no signs of worsening kidney function.

**Comment:** Lupus nephritis afflicts 45% of patients with systemic lupus erythematosus, with 10%–30% of patients with lupus nephritis progressing to kidney failure within 15 years of diagnosis. The current standard care is MMF and low-dose glucocorticoids. Voclosporin is a second-generation calcineurin inhibitor approved in some countries for treating adults with active lupus nephritis, combined with standard immunosuppressive therapy. Phase 2 and phase 3 studies have demonstrated improved proteinuria with voclosporin. This post hoc analysis of the phase 3 AURORA 1 clinical trial evaluated the efficacy and safety of voclosporin in a subgroup of patients with proliferative lupus nephritis and high levels of proteinuria. Results showed a significantly higher percentage of complete and partial kidney responses, supporting its use for this indication. The limitation of this post hoc analysis was the short follow-up, given that this sub-group of patients generally have poorer outcomes and that this study was not powered to detect differences in treatment outcomes for this subset of patients. Despite this, this analysis suggests that voclosporin is an effective therapy in this “difficult to treat” population. Further studies targeting this subgroup are needed.

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**Metabolic acidosis in CKD – to treat or not to treat? Still an unresolved mystery**

**VALOR_CKD: A Multicenter, Randomized, Double-Blind Placebo-Controlled Trial Evaluating Veverimer in Slowing Progression of CKD in Patients with Metabolic Acidosis**


Reviewed by Sara Ksiazek

**Summary:** In this phase 3 trial, the novel hydrochloric acid binder, veverimer, was evaluated in patients with chronic kidney disease (CKD, eGFR 20-40ml/min/1.73m²) and metabolic acidosis (serum bicarbonate 12-20mEq/L) for the slowing of CKD progression. Part A of this study consisted of a 4-8 week active treatment run-in period where all participants (n=2198) received veverimer, and those who showed an increase in serum bicarbonate by ≥ 4 mEq/L or a serum bicarbonate ≥ 22 mEq/L progressed to the next stage. In Part B of the study, 1480 participants were randomized to either veverimer (n=741) or placebo (n=739) and followed up for a median of 2.2 years. At baseline, the mean eGFR was 29.2 ± 6.3ml/min/1.73m², and the mean serum bicarbonate was 17.5 ± 1.4 mEq/L. After the active run-in period, the mean serum bicarbonate level rose to 23.4 ± 2.0 mEq/L. After 3 months of randomization the patients in the veverimer group had a serum bicarbonate of 22.0 ± 3.0 mEq/L and the placebo group of 20.9 ± 3.3 mEq/L, resulting in a difference of 1.1 mEq/L (P < 0.001) between the groups. This difference remained constant throughout the 2-year follow-up. The primary outcome of CKD progression, defined as the development of ESKD (kidney transplantation or maintenance dialysis), a sustained decline in eGFR of ≥ 40% from baseline, or death due to kidney failure, was similar in both groups with an occurrence of 149/741(9.9%) and 148/739 (9.6%) in the veverimer and placebo groups respectively (HR 0.99; 95% CI, 0.8 to 1.2; P=0.90). The incidence of adverse events did not differ between the two groups, including gastrointestinal events or impact on blood pressure. The trial was terminated early in May 2022 due to administrative reasons.

**Comment:** Metabolic acidosis is a common complication of CKD, but well-powered trials have not shown that treating it slows CKD progression. VALOR-CKD, conducted across 320 sites in 35 countries, is one of the largest trials investigating metabolic acidosis in CKD. However, despite the deliberately designed run-in period where only patients meeting the responder criteria could continue to randomization, the study failed to demonstrate the efficacy of veverimer in slowing CKD progression. Unexpectedly, the serum bicarbonate level in the veverimer group dropped by 1.41 mEq/L after randomization, and the difference between the veverimer and placebo groups post-
randomization withdrawal turned out to be smaller than anticipated, with only 1mEq/L difference in serum bicarbonate. This small difference led to negative trial results regarding the primary outcome with no change between the groups. Moreover, the trial was terminated early, but it is unlikely that a longer duration of follow-up would have changed the primary or secondary findings. Nevertheless, the authors should be commended for publishing the negative trial results as it led to the 2024 KDIGO clinical practice guidelines downgrading their recommendations for the treatment of metabolic acidosis in CKD to a practice point, suggesting treatment to keep serum bicarbonate levels > 18 mEq/L. For now, we remain without evidence that treatment of metabolic acidosis improves kidney function. Future trials should target a greater serum bicarbonate separation between the active and treatment groups, and consider a longer run-in period to ensure chronicity of metabolic acidosis.

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**ISN Academy: Chronic Kidney Disease**

**Personalized algorithm based on the patient’s electronic health record can be used to identify patients and deliver evidence-based interventions**

Pragmatic Trial of Hospitalization Rate in Chronic Kidney Disease


Reviewed by Nayaf Habashi

**Summary:** This is a cluster-randomized, open-label, multicenter study that involved 11,182 patients who had the kidney-dysfunction triad (defined as chronic kidney disease (CKD), type 2 diabetes, and hypertension) treated across 141 primary care clinics. The intervention group (n = 71 practices, 5690 patients) used a personalized algorithm embedded in the electronic health record (EHR) to identify participants in real-time, and practice facilitators assisted primary care providers in delivering evidence-based interventions (e.g. updating problem list, targeting clinic BP <140/90mmHg, prescribing ACEi/ARB, minimizing nonsteroidal drug use). The control group (n = 70 practices, 5492 patients) received usual care, which did not allow access to practice facilitators or trial material. At 1 year, the hospitalization rate for any cause in the intervention group was 20.7% (95% CI, 19.7-21.8), and 21.1% (95% CI, 20.1-22.2) in the control group. The difference between groups of 0.4% was not statistically significant (P=0.58). The risks of emergency department visits, readmissions, cardiovascular events, dialysis, or death from any cause at 12 months were similar between the two groups. In addition, more participants in the intervention group had an updated problem list, had documented the delivery of patient education regarding CKD, hypertension, diabetes and cardiovascular risk, had documented goal targets for blood pressure and diabetes, and had added new treatments for these conditions than the control group. The risk of adverse events was also similar in both groups, with the most common adverse event reported as acute kidney injury (AKI), occurring in 12.7% of participants in the intervention group and 11.3% in the control group.

**Comment:** The study's findings suggest that the intervention using EHR-based algorithms and practice facilitators is an innovative approach to managing high-risk patients. The intervention aimed to optimize treatment for high-risk patients, including minimizing nonsteroidal drug use, ensuring appropriate dosing, and managing multiple medications. The study found no significant difference in the primary endpoint (hospitalization rates) between the intervention and usual care groups at 12 months. However, the results might be limited by the short follow-up period (1 year) and the low utilization of beneficial medications such as SGLT2 inhibitors and GLP-1 receptor agonists at baseline with no reporting of their uptake in follow-up. Therefore, future research with extended follow-up periods of at least 2-3 years is recommended to assess such strategies' long-term benefits and potential complications accurately.

Edited by Neeru Agarwal, Megan Borkum, Michele Provenzano, and Anastasiia Zykova