Adding Mineralocorticoid Receptor Antagonists to SGLT2 Inhibitors: Should We Push the Envelope?

By Micah Schub and Matthew A. Sparks

In recent years, the addition of sodium glucose co-transporter 2 (SGLT2) inhibitors to maximally tolerated renin-angiotensin system (RAS) blockade for the treatment of diabetic and non-diabetic proteinuric kidney disease has been a monumental development for the field of nephrology. Both the CREDENCE and DAPA-CKD trials showed a significant reduction in a composite kidney outcome (doubling of serum creatinine, progression to end stage kidney disease, and death from kidney or cardiovascular causes) and a reduction in albuminuria (1, 2). Similarly, in the recent FIDELIO-DKD and FIGARO-DKD trials, use of the non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone showed a significant reduction in a composite kidney outcome and a reduction in albuminuria (3, 4). Post hoc analyses of these trials showed that the nephroprotective effects of both drug classes (SGLT2 inhibitors and MRAs) may be complementary, even in addition to RAS blockade. However, these analyses were post hoc and did not address albuminuria reduction. Moreover, questions remain whether traditional steroidal MRAs (spironolactone or eplerenone), which are less expensive, would provide the same benefit as non-steroidal MRAs (finerenone).

The Rotation for Optimal Targeting of Albuminuria and Treatment Evaluation (ROTATE)-3 study, recently published in *JASN* (5), randomized 46 patients, aged ≥18 years, with urinary albumin excretion ≥100 mg per 24 hours and ≤3500 mg per 24 hours; with an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2; with serum potassium ≤5 mmol/L; and who were on stable doses of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) for more than 4 weeks. The study used three consecutive open-label crossover treatment periods of 4 weeks each, in which patients were treated with the MRA eplerenone 50 mg once daily, the SGLT2 inhibitor dapagliflozin 10 mg once daily, or a combination of eplerenone 50 mg once daily and dapagliflozin 10 mg once daily.

The primary outcome was change in the urinary albumin-to-creatinine ratio (UACR) from baseline between treatments. The baseline mean UACR in all participants was 401 mg/g. After 4 weeks of treatment, reduction in albuminuria was greatest in the combined dapagliflozin-eplerenone period (–53%), then the eplerenone period (–33.7%), followed by the dapagliflozin period (–19.6%). Interestingly, there was no association between individual UACR change during the individual dapagliflozin and eplerenone periods (r = 0.07; p = 0.63). There was a significant increase in potassium in the eplerenone period (+0.36 mmol/L), but this appeared to be blunted by addition of dapagliflozin in the dapagliflozin-eplerenone period (+0.23 mmol/L).

Persistent albuminuria and poor response to treatment are associated with risk of kidney disease progression and poor cardiovascular outcomes. The ROTATE-3 study suggests that the combination of SGLT2 inhibitors and MRA, in addition to maximal RAS blockade, is better at reducing albuminuria than either treatment alone. Importantly, patients showed a varied response to the different classes of medicines, indicating that patients who do not respond to one treatment may benefit from the other. Intriguingly, the addition of SGLT2 inhibitors to MRA therapy may reduce the incidence of hyperkalemia, potentially improving the safety profile of MRAs.

These findings support the need for large randomized controlled trials assessing clinical outcomes of these two medication classes in combination. Moreover, traditional steroidal MRAs can be considered until direct comparison studies are performed with the novel non-steroidal MRA finerenone, unless patients are not able to tolerate steroidal MRAs. The ROTATE-3 study sheds light on this important clinical conundrum. The next era of kidney disease treatment is coming into focus and appears to be triple therapy: RAS blocker, SGLT2 inhibitor, and MRA. ■

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Albuminuria-lowering effect of dapagliflozin, eplerenone, and their combination in patients with CKD

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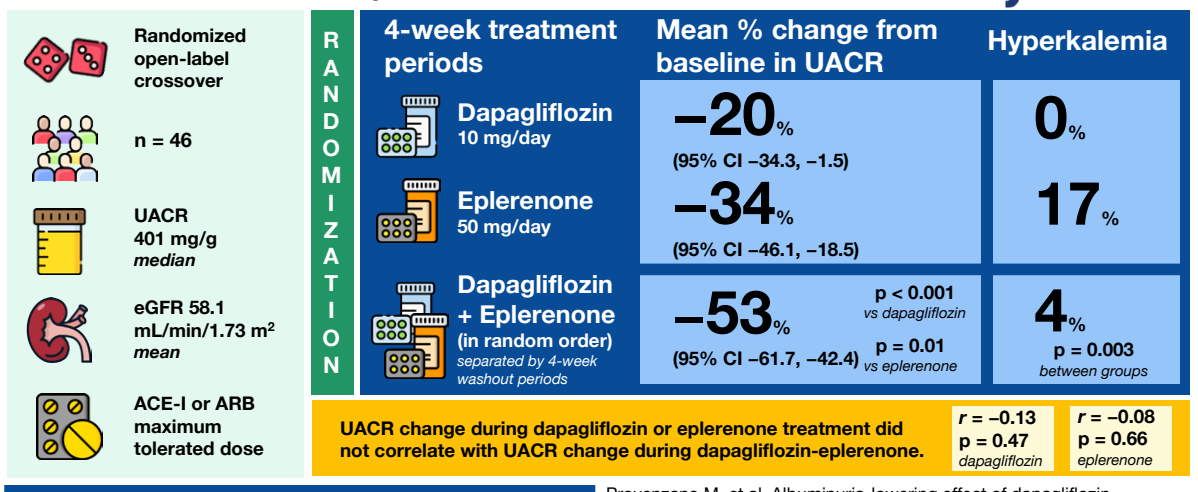

Conclusions: Albuminuria changes in response to dapagliflozin and eplerenone did not correlate, supporting systematic rotation of these therapies to optimize treatment. Combining dapagliflozin with eplerenone resulted in a robust, additive, UACR-lowering effect. CKD, chronic kidney disease.

Provenzano M, et al. Albuminuria-lowering effect of dapagliflozin, eplerenone, and their combination in patients with chronic kidney disease: A randomized crossover clinical trial. *JASN* 2022; 33:1569–1580. doi: 10.1681/ASN.2022020207

Visual Abstract by Edgar Lerma, MD, FASN

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Can Anakinra Reduce Inflammation in Hemodialysis?

By Latoya Gayle and Jeffrey Silberzweig

Inflammation is implicated in the pathogenesis of cardiovascular disease and protein-energy wasting, which are important contributors to morbidity and mortality of patients with end stage kidney disease. It has been postulated that suppressing inflammation with anti-cytokine therapy may improve inflammation and related outcomes.

ACTION, a parallel group, double-blind, randomized placebo-controlled pilot trial, evaluated the efficacy, safety, and tolerability of anakinra in hemodialysis patients (1). Eighty patients were randomized to receive anakinra or placebo via their hemodialysis circuit, three times weekly for 24 weeks and then followed for an additional 24 weeks. Highly sensitive C-reactive protein (hsCRP), interleukin (IL)-6, IL-10, IL-1β, tumor necrosis factor-α, and white cell count were collected pre-dialysis at two screening visits and at follow-up visits every 4 weeks (1). Anakinra was well tolerated, with similar adverse events in both arms. Notably, there were no infectious complications, despite the fact that anakinra can reduce the ability to control infections and can cause leukopenia. IL-6 levels decreased significantly in the treatment group with no change in the placebo arm. There was also a greater reduction in hsCRP in the anakinra group; however, the decrease was not statistically significant. Because of the short duration of the study, hard endpoints, such as cardiovascular events and changes in weight, were not examined. The ACTION trial suggests that the use of anakinra to reduce inflammation in patients treated by maintenance hemodialysis is safe, well tolerated, and feasible. The small study size and uniform age distribution limit generalizability of the results. None of the enrolled patients received dialysis via catheters, which may contribute to inflammation; thus, further study is necessary.

The findings of the ACTION trial provide a new outlook into the potential for treatment of inflammation with anti-cytokine therapy in patients receiving maintenance hemodialysis. Further study is needed to assess how these findings trans-