Complement Inhibitors for the Treatment of C3G

Continued from page 13

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Finerenone: Completing the Cardiorenal Guideline-Directed Medical Therapy?

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Heart failure (HF) and chronic kidney disease (CKD) are often a concurrent diagnosis; almost 50% of patients with HF experience kidney dysfunction, and HF is prevalent in 17%–50% of patients with CKD (1). Kidney function is an independent predictor for inpatient mortality of patients with acute HF, length of hospital stay, and readmission rate (2). Finerenone, a nonsteroidal mineralocorticoid antagonist (MRA), has proven efficacy in reducing kidney disease progression, albuminuria, and cardiovascular events (including hospitalization for HF) in patients with CKD and type 2 diabetes, whereas steroidal MRAs reduce morbidity and mortality among patients with HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (3, 4). Given significant overlap of HF and CKD along with therapeutic benefits of MRAs in these individual diseases, two recent studies in *The New England Journal of Medicine* (5) and the *Journal of the American College of Cardiology* (6) explored cardiac and renal outcomes associated with finerenone in patients with HFpEF and HF with moderately reduced EF (HFmrEF).

In *The New England Journal of Medicine*, Solomon et al. (5) conducted an international, double-blind study that evaluated composite outcomes of worsening HF events, including hospitalizations and mortality, in patients treated with finerenone versus placebo (FINEARTS-HF). Their results showed a significant reduction in primary outcome events for the finerenone group compared with placebo (relative risk, 0.84; 95% confidence interval [CI], 0.74–0.95), although improvement in New York Heart Association classification scores at 12 months was not statistically significant (odds ratio, 1.01; 95% CI, 0.88–1.15). They also assessed kidney composite outcomes, including a more than 50% decline in the estimated glomerular filtration rate (eGFR), initiation of long-term dialysis, or kidney transplantation. Finerenone was not associated with an improvement in kidney composite outcome, although it is pertinent to note that these patients were at low risk for kidney disease progression given low prevalence of albuminuria. The trial had the following limitations:

- Low enrollment of Black patients was attributed to global distribution, although the authors state that it was proportional to the population percentage on a regional basis.
- The prespecified subgroups were underpowered, so the results of the subgroup analysis should be interpreted with caution.
- It cannot be deduced that benefits could be redemonstrated with other MRAs.

A study ascertaining kidney outcomes in the FINEARTS-HF cohort was simultaneously published in the *Journal of the American College of Cardiology* and specifically addressed sustained ≥50% eGFR decline or kidney failure (sustained eGFR decline, <15 mL/min/1.73 m^2); initiation of maintenance dialysis; renal transplant; eGFR slope; and changes in the urine albumin/creatinine ratio (6). Albuminuria was a predictor of adverse cardiovascular and kidney outcomes in HFmrEF and HFpEF (7). The authors found that those assigned to finerenone had an initial acute decline in eGFR from baseline to month 3, although it did not alter the eGFR slope chronically. Finerenone reduced urine albumin/creatinine ratio by 30% (95% CI, 25%–34%) over 6 months versus placebo, an effect that persisted throughout follow-up—a pertinent finding that likely has long-term implications for the development of kidney failure. In addition, it reduced the risk of new onset of microalbuminuria by 24% (hazard ratio, 0.76; 95% CI, 0.68–0.83) and macroalbuminuria by 38% (hazard ratio, 0.62; 95% CI, 0.53–0.73). The long-term effect of this reduction in onset of albuminuria and levels could not be assessed due to short-term follow-up associated with the study.

Although both studies report hyperkalemia as an adverse effect of finerenone, neither assessed it in depth. There is lack of robust guidelines on the frequency of a potassium measurement postdrug commencement and characteristics that portend a higher risk of hyperkalemia.

In light of the above findings, finerenone has the potential to become an essential component of the cardiorenal goal-directed medical therapy in populations that have a high proportion of overlap of CKD and HF, especially after the success of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 agonists (2). A few questions remain:

- When is the ideal time to commence finerenone, and where does it stand in the sequence of sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 agonists?
- Is finerenone going to be beneficial when treating patients established on the aforementioned drugs?
- Is the reduction in onset of albuminuria and levels in patients with established HFmrEF and HFpEF (and therefore preventing development of CKD) going to correlate with optimal long-term cardiac and renal outcomes? Although the answer to this is intuitively positive, follow-up data from these trials are required.

In conclusion, we are progressively entering an era in which two diseases (CKD and HF) can be treated with multiple agents. Whereas nephrology was a bit late to the concept of guideline-directed medical therapy, it has certainly arrived and will be carrying the baton going forward. ■

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