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Letter to the Editor

Letter to the editor regarding "Patiromer and Sodium Zirconium Cyclosilicate in Treatment of Hyperkalemia: A Systematic Review and Meta-analysis: Patiromer and Sodium Zirconium Cyclosilicate in Hyperkalemia'

Dear Dr. Walson:

We read the review by Shrestha et al[1] with both interest and concern. We are concerned that the methodology employed omits important datasets, making some of the conclusions inaccurate and misleading.

First, the data included in the meta-analysis and systematic review omits all nondialysis Phase III registration trials for sodium zirconium cyclosilicate (SZC) (Lokelma; AstraZeneca Pharmaceuticals LP, Wilmington, Delaware), including Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE), HARMONIZE extension, and ZS-005.[2–4] Furthermore, the authors erroneously included a subgroup analysis of HARMONIZE rather than the primary analysis and mislabeled another study, HARMONIZE-Global, as HARMONIZE.[5,6] Although HARMONIZE extension (ZS-004E) and ZS-005 were omitted from the meta-analysis because they were not comparative studies, they still provide important and clinically relevant information for SZC.[3,4] Exclusion of such studies biases the conclusions and does not reflect accurately on the totality of data used to gain a successful registration status for SZC.

Second, with regard to the sodium content of SZC and the adverse event of edema, in the discussion section the authors state, "The most prominent side effect noted with sodium zirconium was edema" and then speculate on the mechanism for this adverse event as well as possible downstream effects without supporting references. It should be noted that SZC preferentially captures potassium in exchange for both hydrogen and sodium.[8,9] Each 5 g sachet of SZC contains approximately 400 mg sodium ion[7]; however, the amount of sodium released and subsequently absorbed per a given dose of SZC has not been quantified. In placebo-controlled trials in which patients received once-daily SZC for up to 28 days, the incidence of edema was 4.4%, 5.9%, and 16.1% with SZC 5 g, 10 g, and 15 g, respectively, compared with 2.4% with placebo.[7] Edema was generally mild to moderate in severity, and in up to 47% of patients, resolved without treatment.[7,8] The remainder were managed with diuretic initiation or diuretic dose adjustment. Of note, in the 2 long-term studies that evaluated the efficacy and safety of SZC for up to 1 year, 2 of 751 patients enrolled in ZS-005 and 0 of 123 patients enrolled in HARMONIZE-Extension discontinued SZC due to edema. The omission of such details results in an unbalanced view of SZC.

Last, the authors conclude that SZC is the drug of choice in patients with acute hyperkalemia, whereas patiromer is the drug of choice in patients with chronic hyperkalemia. They base their recommendations on SZC's rapid onset of action and the occurrence of edema in some patients. These recommendations are not based on clinical data and are contradictory to the authors' conclusion that "both patiromer and sodium zirconate [sic] were found safe in the treatment of hyperkalemia" and are thus misleading. International Phase III clinical trials have demonstrated the safety and efficacy of SZC for up to 12 months among patients with multiple comorbidities, including chronic kidney disease (CKD), heart failure, and diabetes mellitus[2–4] as well as in patients with mild, moderate, severe, or end-stage CKD.[7–9] All of these studies were published within the search period of this review. Additionally, the 2020 and 2021 Kidney Disease: Improving Global Outcomes Clinical Practice Guidelines, the 2021 European Society of Cardiology Guidelines, and the 2021 American College of Cardiology Expert Consensus Decision Pathway include both SZC and patiromer as treatment options for the management of hyperkalemia in patients with CKD and heart failure.[10–13] Neither therapeutic agent has a limitation of use with regard to duration of treatment.

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