Effectiveness of Sodium Zirconium Cyclosilicate in Hemodialysis Patients With Severe Hyperkalemia

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Severe hyperkalemia is often defined as predialysis serum potassium (sK+) concentration $\geq 6.0$ mmol/l and is associated with a greater risk of hospitalization, major adverse cardiovascular events, and all-cause mortality versus referent predialysis sK+ concentrations.1,2

Several approaches are available for managing potassium homeostasis in hemodialysis patients. A challenge in selecting an appropriate dialysate potassium concentration is balancing removal of potassium to avoid hyperkalemia while minimizing the risk of adverse events associated with lowering potassium too rapidly. The use of nondialytic measures, such as potassium binders during the interdialytic period, to improve potassium homeostasis decreases the need to expose patients to a dialysate with low potassium concentrations.3

Sodium zirconium cyclosilicate (SZC) is a novel, highly selective potassium binder that preferentially captures potassium in the gastrointestinal lumen, increasing potassium fecal excretion and thereby reducing sK+ concentration.4,5 The phase IIIb DIALIZE study (NCT03303521) revealed that SZC is an effective and well-tolerated treatment for hyperkalemia in patients with end-stage kidney disease undergoing maintenance hemodialysis.6 Here, we report the results of a post hoc analysis of DIALIZE that assessed the efficacy of SZC versus placebo in patients with severe hyperkalemia (predialysis sK+ concentration $\geq 6.0$ mmol/l) at baseline.

RESULTS

Patients

In DIALIZE, at baseline (visit 1, day −7), 88 patients (SZC n = 46, placebo n = 42) had predialysis sK+ concentration $\geq 6.0$ mmol/l and 106 patients (SZC n = 49, placebo n = 57) had predialysis sK+ concentration <6.0 mmol/l (Supplementary Results and Supplementary Table S1).

Treatment Responders

Treatment responders were defined as patients who, during the 4-week evaluation period, maintained target predialysis sK+ concentration for $\geq 3$ of 4 hemodialysis treatments after the long interdialytic interval (LIDI) and did not require rescue therapy to lower sK+ concentration. Among patients with baseline severe hyperkalemia, the proportions of treatment responders were significantly greater with SZC versus placebo using target predialysis sK+ ranges of 4.0 to 5.0 mmol/l (34.8% vs. 0%, respectively; Figure 1a) and an extended range of 4.0 to 5.5 mmol/l (67.4% vs. 19.0%, respectively; Figure 1b) (both $P < 0.0001$ for SZC vs. placebo). For patients receiving SZC, there was no statistical difference between baseline predialysis sK+ $\geq 6.0$ mmol/l versus <6.0 mmol/l subgroups in responder rates using a target predialysis sK+ range of 4.0 to 5.0 mmol/l (34.8% vs. 46.9%, respectively; $P = 0.2974$) and an extended range of 4.0 to 5.5 mmol/l (67.4% vs. 71.4%, respectively; $P = 0.8239$).
Patients Achieving Target sK⁺ Concentrations
In the baseline severe hyperkalemia subgroup, the proportions of patients achieving target predialysis sK⁺ ranges at ≥1, ≥2, ≥3, and 4 LIDI visits in the 4-week evaluation period were greater with SZC versus placebo at both target predialysis sK⁺ ranges (Figure 2a and b). In the baseline severe hyperkalemia subgroup, 17.4% and 47.8% of patients receiving SZC achieved target predialysis sK⁺ ranges of 4.0 to 5.0 mmol/l and 4.0 to 5.5 mmol/l at all 4 LIDI visits, respectively, versus 0% and 2.4% of patients receiving placebo, respectively (Figure 2a and b). Logistic regression analysis indicated that differences in the proportions of patients achieving target predialysis sK⁺ ranges at ≥1, ≥2, ≥3, and 4 LIDI visits were significant for SZC versus placebo, based on 95% CIs not crossing 0% (Figure 2a and b).

Predialysis sK⁺ Concentrations
With both SZC and placebo, mean predialysis sK⁺ concentrations over the LIDI visits in the 4-week evaluation period were numerically greater for patients with baseline predialysis sK⁺ ≥6.0 mmol/l than those with <6.0 mmol/l. Mean predialysis sK⁺ concentrations were consistently and significantly lower with SZC versus placebo in both baseline predialysis sK⁺ subgroups (P < 0.0001 for SZC versus placebo at each LIDI visit) (Supplementary Figure S1).

Hypokalemia
The frequency of predialysis hypokalemia (sK⁺ <3.5 mmol/l) was low overall (Supplementary Table S3). The proportions of patients with hypokalemia were numerically higher with SZC in the baseline predialysis sK⁺ <6.0 mmol/l subgroup than ≥6.0 mmol/l subgroup (Supplementary Table S3).

DISCUSSION
To the best of our knowledge, this is the first assessment of the efficacy of a potassium binder in maintenance hemodialysis patients with severe hyperkalemia (predialysis sK⁺ concentration ≥6.0 mmol/l) based on data from a randomized controlled trial. Among the patients with severe hyperkalemia, the rates of treatment response were significantly greater with SZC versus placebo, regardless of target predialysis sK⁺ range used (i.e., 4.0–5.0 mmol/l or 4.0–5.5 mmol/l). Among the patients receiving placebo with severe hyperkalemia, mean predialysis sK⁺ concentrations over 4 weeks remained at approximately 6.0 mmol/l, indicating without additional strategies these patients
continued to be at risk of persistent severe hyperkalemia and associated adverse events.\textsuperscript{1,2}

Among SZC-treated patients, the extended predialysis s$K^+$ range of 4.0 to 5.5 mmol/l reduced the impact of severe hyperkalemia on the efficacy outcomes evaluated. Findings from the treatment responder analysis indicate that some SZC-treated patients had reductions from baseline in predialysis s$K^+$ concentration but were not deemed as responders using the target predialysis s$K^+$ range of 4.0 to 5.0 mmol/l because their s$K^+$ concentration was between 5.0 mmol/l and 5.5 mmol/l. Nevertheless, the extended predialysis s$K^+$ range of 4.0 to 5.5 mmol/l reflects one deemed to be acceptable in clinical practice, while avoiding concentrations >5.5 mmol/l associated with increased hospitalization and mortality.\textsuperscript{2} These findings suggest that, among hemodialysis patients with severe hyperkalemia, SZC lowers and maintains predialysis s$K^+$ concentrations to a clinically acceptable range in most patients over 4 weeks.

The frequency of predialysis hypokalemia events was low overall and generally comparable for SZC and placebo. The events of postdialysis hypokalemia were numerically greater with SZC versus placebo, and among the baseline predialysis s$K^+$ concentration range 4.0 to 6.0 mmol/l versus ≥6.0 mmol/l subgroups, consistent with the potassium-lowering effects of SZC in addition to hemodialysis and the smaller reduction in s$K^+$ required to meet the hypokalemia threshold, respectively.

A challenging aspect of hyperkalemia management is the lack of a standardized definition for the grading of severity.\textsuperscript{7,8} Collectively, there is consensus to immediately assess and treat patients with severe hyperkalemia.\textsuperscript{7,8} The recent Renal Association Clinical Practice Guidelines on Hemodialysis recommend maintaining a predialysis s$K^+$ concentration range of 4.0 to 6.0 mmol/l,\textsuperscript{9} as a s$K^+$ concentration ≥6.0 mmol/l is associated with a greater risk of hospitalization and all-cause mortality.\textsuperscript{1} Nevertheless, the increased rates of hospitalization and mortality associated with predialysis s$K^+$ concentration >5.5 mmol/l\textsuperscript{2} challenge the use of a target of 6.0 mmol/l. In our analysis, nearly two-thirds of hemodialysis patients with severe hyperkalemia were at risk of persistent severe hyperkalemia and associated adverse events.\textsuperscript{1,2}

Figure 2. Proportions of patients with target predialysis s$K^+$ range of (a) 4.0 to 5.0 mmol/l and (b) 4.0 to 5.5 mmol/l at ≥1, ≥2, ≥3, and 4 LIDI visits and corresponding mean s$K^+$ concentrations, by baseline predialysis s$K^+$ subgroup. Visit 1 (day –7) predialysis s$K^+$ measurement was used as baseline. Only s$K^+$ data from LIDI visits during the evaluation period (days 36, 43, 50, and 57) were used. Patients who received rescue therapy were included. Percentages were calculated for each treatment arm using the number of patients in each predialysis s$K^+$ subgroup at baseline as the denominator; no imputation of missing data was conducted. s$K^+$ concentrations are overall mean (SD) for patients with target predialysis s$K^+$ range at ≥1, ≥2, ≥3, or 4 LIDI visits. LIDI, long interdialytic interval; s$K^+$, serum potassium; SZC, sodium zirconium cyclosilicate.
hyperkalemia receiving SZC achieved a target predialysis Sk⁺ concentration range of 4.0 to 5.5 mmol/l for ≥3 of 4 hemodialysis treatments after the LIDI and will be expected to be at lower risk of adverse events associated with higher predialysis Sk⁺ concentrations.

These analyses have limitations. The analyses are post hoc and were not prespecified; therefore, the results are exploratory. Patient numbers within each predialysis Sk⁺ subgroup were small and not powered to investigate treatment associations, which limits the interpretation of our findings. Finally, we did not evaluate the impact of severe hyperkalemia on safety outcomes, such as cardiovascular events. Regarding this point, the DIALIZE-Outcomes study (EudraCT 2020-005561-14) will evaluate the effect of SZC on arrhythmia-related cardiovascular outcomes among chronic hemodialysis patients with recurrent hyperkalemia (predialysis Sk⁺ concentration ≥5.5 mmol/l).

In conclusion, these post hoc findings suggest that SZC could be an effective addition to maintenance hemodialysis in reducing predialysis Sk⁺ concentration in patients with end-stage kidney disease and severe hyperkalemia who are at high risk of adverse events.

The extended target predialysis Sk⁺ range of 4.0 to 5.5 mmol/l seemed to negate the impact of severe hyperkalemia. Evidence of the effectiveness of SZC in this subgroup of DIALIZE has clinical relevance and potential applicability beyond the tight confines of a clinical trial setting.

**DISCLOSURE**

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DATA SHARING

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca’s data-sharing policy described at https://astrazenecagroup-dt.pharmacm.com/DT/Home.

AUTHOR CONTRIBUTIONS

All authors contributed to the data interpretation, critically reviewed the manuscript, approved the final version, and accept accountability for the overall work.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary Methods.
Supplementary Results.
Supplementary References.

Table S1. Baseline patient characteristics by baseline predialysis sK⁺ subgroup (<6.0 mmol/l and ≥6.0 mmol/l).

Table S2. Doses of SZC and placebo at the end of the dose titration period, by baseline predialysis sK⁺ subgroup (<6.0 mmol/l and ≥6.0 mmol/l).

Table S3. Events of pre- and post-dialysis hypokalemia (sK⁺ <3.5 mmol/l), by baseline predialysis sK⁺ subgroup (<6.0 mmol/l and ≥6.0 mmol/l).

Figure S1. Mean predialysis sK⁺ concentrations at LIDI visits during the 4-week evaluation period by treatment arm and baseline predialysis sK⁺ subgroup (≥6.0 mmol/l and <6.0 mmol/l).

STROBE Statement (PDF).

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