A New Treatment for Hyperkalemia at Last?

In new trials, ZS-9 looks safe and effective for outpatient potassium reduction

Nephrologists have been waiting decades for a safe and effective new option to lower potassium in patients with hyperkalemia. Now, two new randomized controlled trials have reported highly encouraging results with a new selective cation exchanger, sodium zirconium cyclosilicate (ZS-9), as an outpatient treatment for hyperkalemia.

“We found that treatment with ZS-9 normalized potassium within 24 hours in the vast majority of patients with hyperkalemia, and maintained normal potassium levels through four weeks of outpatient treatment,” said Edgar Lerma, MD, of University of Illinois Chicago Advocate Christ Medical Center. Lerma was one of the authors of the HARMONIZE (Hyperkalemia RandoMized interventiON multI-dose ZS-9 maintEinance) trial, which was simultaneously presented at the American Heart Association Scientific Sessions and published in the *Journal of the American Heart Association* in November.

**Two pivotal trials of new hyperkalemia therapy**

The HARMONIZE trial, or ZS-004, was released the same week as the preceding ZS-003 trial, which was published in the *New England Journal of Medicine*. Collectively, the two trials evaluated more than 1000 patients with hyperkalemia, according to Mikhail Kosiborod, MD, a cardiologist at Saint Luke’s Mid America Heart Institute in Kansas City, MO, and lead author of HARMONIZE. “Current treatments of hyperkalemia have significant shortcomings,” said Kosiborod. “Together, the results of these new studies indicate that ZS-9 is highly efficacious in rapidly reducing potassium levels and maintaining normokalemia for up to four weeks.”

Added Kosiborod: “These results have the potential to shift the current paradigm for how hyperkalemia is managed among various at-risk patient groups.” Both trials were sponsored by ZS Pharma, Inc.

The multicenter HARMONIZE trial included 258 outpatients with hyperkalemia, defined as a baseline potassium level of 5.1 mEq/L or higher. In an initial open-label phase, all patients were treated with oral ZS-9: 10 g three times daily. The response was dramatic, with 237 patients reaching normal potassium levels of 3.5 to 5.0 mEq/L. Potassium dropped significantly within 1 hour after the first dose of ZS-9. The median time to normokalemia was 2.2 hours, with 84 percent of patients reaching normal levels by 24 hours and 98 percent by 48 hours.

The 237 responders were then randomly assigned to 28 days of treatment with ZS-9, at a dose of 5, 10, or 15 g per day, or placebo. During treatment, potassium levels were 4.8, 4.5, and 4.4 mEq/L, respectively, in the active treatment groups, compared with 5.1 mEq/L with placebo.

Potassium levels remained in the normal range in 80 percent of patients receiving the 5-g dose, 90 percent of those receiving the 10-g dose, and 94 percent of those receiving the 15-g dose of ZS-9, compared with 46 percent of the placebo group during the randomized phase. Adverse events were similar between groups, although the rate of edema was numerically higher with the 15-g dose of ZS-9. The rate of gastrointestinal adverse events was numerically lower in patients receiving ZS-9, compared with placebo.

Hypokalemia occurred in about 10 percent of patients receiving the 10-g and 15-g doses, compared with none of those taking ZS-9 5 mg or placebo. “All cases of hypokalemia were mild and responded to protocol-directed dose reduction,” said Lerma. “Thus we have a product that consistently lowered potassium across all patient subgroups, with excellent tolerability similar to placebo.”

The ZS-003 trial, a separate and larger trial, in which the primary endpoint was focused on the short-term 48-hour efficacy of ZS-9 compared with placebo, showed comparable 48-hour reductions in potassium levels with ZS-9 among 753 patients with hyperkalemia. The lead author was David K. Packham, MB, BS, MD, of
For the control of serum phosphorus levels in patients with chronic kidney disease on dialysis

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in some cases as high as 7.2 mEq/L—in HARMONIZE.

Nephrologists don’t need to be told that progress toward the development of a safe and effective new treatment for hyperkalemia is welcome news. Currently, the main option for treatment of hyperkalemia is sodium polystyrene sulfonate (SPS), also known asKayexalate. Approved before the passage of the Kefauver-Harris Drug Amendments in 1958, SPS is a “grandfathered” drug that to this day has shown little or no evidence of efficacy in reducing potassium levels. Subsequent safety concerns have included uncommon cases of colonic necrosis linked to a widely used preparation of SPS plus sorbitol. A landmark 50-year review by Richard Sterns, MD, of the University of Rochester, published in the Journal of the American Society of Nephrology in 2010, questioned whether SPS would have ever been approved under the current U.S. Food and Drug Administration (FDA) standards. Another study published in the American Journal of Medicine in 2013 noted the association between SPS, with or without sorbitol, and gastrointestinal injury. “Since the publication of these articles and other case reports, I have limited use of SPS to extreme circumstances in my clinical practice, particularly because of concerns about gastrointestinal adverse events, such as colonic necrosis,” Lerma said.

Hyperkalemia is a common disorder, which carries a risk of life-threatening cardiac arrhythmias and other adverse outcomes. It is commonly seen in patients with chronic kidney disease, heart failure, and diabetes mellitus. The same conditions are important indications for renin-angiotensin-aldosterone system (RAAS) inhibitors, for which elevated potassium levels are a side effect. Clinicians may hesitate to prescribe RAAS inhibitors for patients with appropriate indications because of the risk of hyperkalemia, Lerma said. “That’s part of the reason why the FDA and many practicing nephrologists are looking for emerging evidence on ZS-9,” he added. “By giving us an effective and safe option for lowering potassium levels, it may help us extend the use of effective treatments for CKD and heart failure.”

The HARMONIZE authors noted some important limitations of their study. It excluded some groups in need of potassium-lowering therapy, including patients receiving dialysis—although they said many patients in their study had stage 4 or 5 chronic kidney disease. Hospitalized patients and those with arrhythmias were also excluded. Further studies are needed to address these groups and to test the long-term efficacy and safety of ZS-9. Long-term outcome studies are ongoing; submission to the FDA is planned during the first half of 2015.

Cuba P. Kovesity, MD, a nephrologist at The University of Tennessee Health Science Center, noted that with modern standards for demonstrating drug efficacy and safety, the supporting data on ZS-9 will be stronger than for previous hyperkalemia treatments. “That will allow us to use it with much greater comfort in patients under various circumstances,” he commented. “That stands both for acute treatment and—most importantly for me as a practicing nephrologist—as a means of managing chronic hyperkalemia.”

While the four-week biochemical results are encouraging, “one would want to learn if similar efficacy is being maintained if patients are taking this for much longer periods—months and years,” Kovesity said. “And this will principally help us determine what we learn in clinical practice.” He noted that with differences in patient selection and adherence, effectiveness in clinical practice may be less than in research trials. Clinical experience will also provide critical information on the safety of ZS-9. “Even though in these relatively short-term studies, the safety profile seems to be adequate, there are rare complications, hypothetically, which may only come to light if much larger numbers of patients take the medication for much longer periods of time.”

And of course, the bottom line is whether ZS-9 and other treatments under development can improve patient outcomes. “I am hopeful that the companies developing these new drugs will invest in further trials, to see if control of hyperkalemia leads to a reduction in sudden cardiac events, for example,” Kovesity said. “Such studies would also tell us if the use of these medications allows a wider use of RAAS inhibitors, which consequently could result in better cardiovascular outcomes.”