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RESEARCH LETTER

Safety and Efficacy of Veverimer in Acidotic Patients With CKD and Heart Failure

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Received 26 April 2021; revised 10 August 2021; accepted 16 August 2021; published online 23 August 2021

Kidney Int Rep (2021) **6,** 2908–2911; https://doi.org/10.1016/j.ekir.2021.08.015

The cumulative risk of heart failure among patients with non–dialysis-dependent chronic kidney disease (CKD) exceeds 40% over 36 months of follow-up.[1] Among more than 118,000 patients hospitalized with acute decompensated heart failure, 64% had an estimated glomerular filtration rate (eGFR) of <60 ml/min per 1.73 m^2.[2]

Low serum bicarbonate (<22 mmol/L), indicating metabolic acidosis, is associated with heart failure.[3] In the failing myocardium, metabolic acidosis reduces cardiac contractility and significantly reduces the contractile force generated by β-adrenergic agonists.[4]

Veverimer is an investigational, oral, non-absorbed polymer designed to treat metabolic acidosis by binding and removing hydrochloric acid from the gastrointestinal tract, leading to an increase in the concentration of serum bicarbonate.[5] It is not an exchange resin and does not introduce unwanted cations (e.g., sodium and potassium) that can be absorbed.[5]

In randomized, blinded, placebo-controlled trials in patients with CKD and metabolic acidosis (Supplementary Figure S1 and Supplementary Table S1), veverimer significantly increased levels of serum bicarbonate and improved physical function.[6–8] The effect of veverimer on serum bicarbonate was similar in patients on proton pump inhibitors or H2 receptor blockers.[6] We hypothesized that veverimer would effectively increase serum bicarbonate without increasing blood pressure, weight, or inducing volume overload–related adverse events in patients with heart failure and metabolic acidosis due to CKD. Here we describe the response to veverimer in the subgroup of patients with heart failure and metabolic acidosis due to CKD who were treated in a randomized, blinded, placebo-controlled trial.[6,7]

RESULTS

Of the 217 randomized patients in the 12-week parent study, 196 were enrolled into the 40-week extension study, 62 of whom were reported to have a history of heart failure (Supplementary Figure S2). Dosing compliance (>80% of prescribed doses taken) was 100% and 99% in the veverimer and placebo groups, respectively. Baseline demographics, comorbidities, serum bicarbonate, eGFR, and blood pressure within the heart failure subgroup and the overall study population were generally balanced across treatment groups (Supplementary Table S2).

Among patients with heart failure, a significantly higher percentage of patients in the veverimer versus the placebo group had a ≥4-mmol/l increase or normalization of serum bicarbonate at week 52 (79% vs. 42%, $P < 0.01$) (Figure 1a), and the mean (standard error [SE]) serum bicarbonate increased by 5.6 (0.6) mmol/l in the veverimer group compared to 2.8 (0.7) mmol/l in the placebo group ($P < 0.01$) (Figure 1b). There was no interaction between treatment and heart failure on this endpoint ($P > 0.05$). These findings were similar to those observed in the overall study population (Figure 1b). The effect of veverimer on serum bicarbonate was evident within 1 week and was sustained through the end of treatment (week 52) (Figure 1c).

Patient-reported physical functioning, as measured by the total score of the Kidney Disease and Quality of Life Instrument—Physical Functioning Domain (KDQoL-PFD), which quantified the extent of limitation in performing daily activities (Supplementary Table S1), improved on veverimer compared with placebo ($P < 0.0001$).[7] The mean (SE) change from randomization to end of treatment in the total score of the KDQoL-PFD within the veverimer group was 11.4 (2.2) points, and the placebo-subtracted treatment effect was 12.1 (3.3) points.[7] On the individual items of the KDQoL, compared

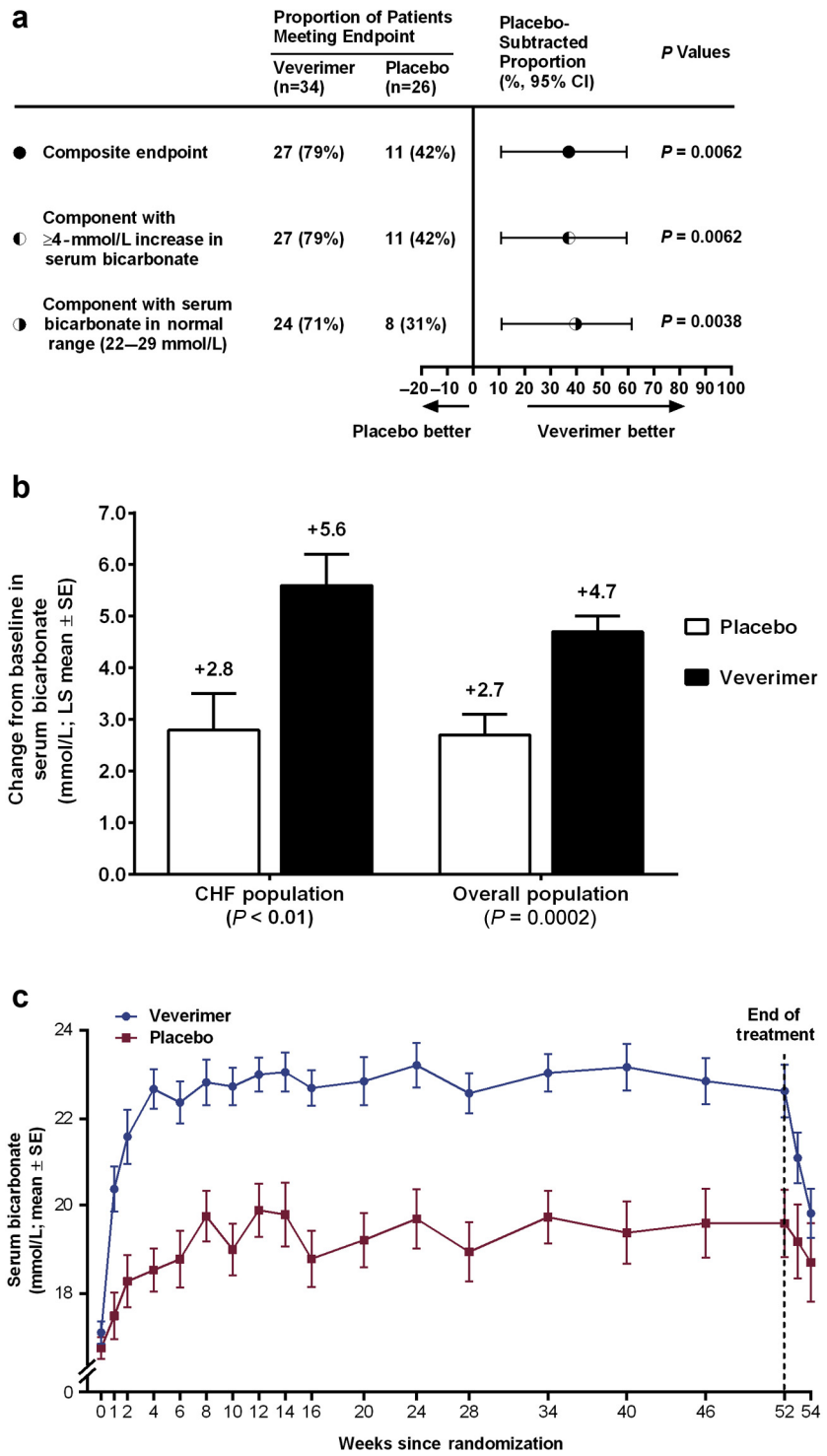

Figure 1. Changes in serum bicarbonate levels. (a) The top line shows the composite endpoint at treatment week 52. The 2 lower lines depict each component of the primary endpoint (percentage of patients who had a ≥4-mmol/L increase or normalization of serum bicarbonate at week 52). *P* values are for the difference in proportions between the veverimer and placebo groups. (b) Change in serum bicarbonate from baseline to week 52. LS, least squares; SE, standard error. (c) Serum bicarbonate levels over time. The baseline serum bicarbonate was 17.1 (0.3) mmol/l and 16.8 (0.3) mmol/l in the veverimer and placebo groups, respectively.

with placebo, veverimer significantly improved the daily activities of climbing a flight of stairs ($P < 0.0001$); walking (1 block [$P = 0.0020$], several blocks [$P = 0.0003$], and more than 1 mile [$P < 0.0001$]); bending, kneeling, or stooping ($P = 0.0113$); and lifting or carrying groceries ($P = 0.0488$).[7] In addition, the mean time for performing the chair stand test decreased from randomization by 4.3 (1.2) seconds on veverimer and by 1.4 (1.2) seconds on placebo [$P < 0.0001$]).[7] There was no interaction of heart failure on the effects of veverimer on either

Table 1. Safety

	Heart failure subgroup[a]		Overall study population[b]	
	Veverimer (n = 34)	Placebo (n = 28)	Veverimer (n = 112)	Placebo (n = 81)
Fatal adverse events	0	1 (3.6%)	0	2 (2.5%)
Serious adverse events	1 (2.9%)	1 (3.6%)	2 (1.8%)	4 (4.9)
Adverse events leading to discontinuation of study drug	0	0	0	1 (1.2%)
Kidney injury-type events[c]	1 (2.9%)	3 (10.7%)	9 (8.0%)	12 (14.8%)
Volume overload, hypertension, and heart failure adverse events				
Congestive heart failure[d]	0	3 (10.7%)	1 (0.9%)	3 (3.7%)
Peripheral edema	0	0	0	1 (1.2%)
Hypertension[e]	1 (2.9%)	0	2 (1.8%)	1 (1.2%)
Blood pressure, weight, and urinary sodium excretion change from baseline to week 52				
Weight (kg)	−0.5 (2.2)	0.4 (2.0)	−0.3 (2.7)	0.5 (2.2)
Systolic BP (mm Hg)	−1.4 (10.0)	−1.9 (7.0)	−2.0 (7.6)	−2.0 (7.1)
Diastolic BP (mm Hg)	−2.3 (9.8)	−1.3 (6.0)	−2.6 (8.0)	−2.9 (5.8)
Urine Na/creatinine ratio (mol/mol)	−0.14 (15.5)	−0.78 (11.1)	−0.11 (13.3)	0.61 (11.0)
Augmentation of diuretics and antihypertensives				
New diuretic or dose increase	2 (5.9%)	4 (14.3%)	7 (6.3%)	6 (7.4%)
New antihypertensives or dose increase	7 (20.6%)	5 (17.9%)	13 (11.6%)	10 (12.3%)

Data presented are mean (SD) or n (%). Adverse events were coded using MedDRA v20.0. BP, blood pressure
[a]Events from the extension study modified intent-to-treat population, defined as patients with a baseline and at least 1 post-baseline bicarbonate value in the parent and extension studies.
[b]Events from the extension study safety analysis population, defined as patients receiving any amount of study drug during this study.
[c]Kidney injury type events are those coded to the Renal and Urinary Disorder System Organ Class. Event preferred terms included renal impairment, chronic kidney disease, acute prerenal failure, azotemia, end-stage renal disease, nephropathy toxic, proteinuria/albuminuria, and renal failure.
[d]Congestive heart failure events included cardiac failure and cardiac failure congestive.
[e]Hypertension events included the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms of hypertension and increased blood pressure.

physical function outcome (rank-based analysis of covariance, $P \geq 0.7$).

Veverimer was well tolerated, with a safety profile that was similar to that of placebo (Table 1). In the heart failure subgroup, fatal, serious, and treatment-limiting adverse events, as well as adverse events relating to heart failure, hypertension, or peripheral edema, were not more common in the veverimer group compared with the placebo group (Table 1).

In the heart failure population, kidney injury−type adverse events were reported in 2.9% of patients in the veverimer group and in 10.7% of patients in the placebo group, which is similar to findings in the overall study population (Table 1). The incidence of heart failure adverse events was 0% in the veverimer group and 10.7% in the placebo group (Table 1). Mean weight, blood pressure, or urine sodium-to-creatinine ratio did not increase in the veverimer group at week 52 relative to baseline. Blood pressure and weight were similar in the veverimer and placebo groups over time (Supplementary Figures S3 and S4). New diuretics were prescribed, or the diuretic dose was increased, in 5.9% and 14.3% of patients in the veverimer and placebo groups, respectively. Augmentation of antihypertensive medications in the 2 groups was similar (Table 1).

DISCUSSION

Treatment with veverimer, an investigational, oral, non-absorbed hydrochloric acid binder, significantly increased serum bicarbonate in patients with congestive heart failure and metabolic acidosis due to CKD, with a safety profile that was similar to that of placebo.

Treatment of metabolic acidosis in patients with heart failure is particularly challenging because sodium-based alkali supplements may precipitate volume overload and cardiac decompensation. Data from the Fourth National Health and Nutrition Examination Survey (NHANES) found that only 37% of patients with CKD and eGFR <60 ml/min per 1.73 m^2 had controlled blood pressure (<130/80 mm Hg).[9] Analyses of data from both the RENAAL and IDNT angiotensin receptor blocker trials found attenuation of the benefits of angiotensin receptor blockers on both renal and cardiovascular outcomes in patients in the highest tertile of sodium intake.[S1]

The mechanism of action of veverimer represents an alternative potential strategy for the treatment of metabolic acidosis, in which acid is bound and removed from the gastrointestinal tract without introducing sodium.[5]

In the cohort of patients with heart failure, veverimer had no adverse effect on volume status. Worsening kidney function increases the risk of heart failure decompensation. Wesson *et al*. previously reported significantly better outcomes in the veverimer versus placebo group with respect to the composite measure of death, dialysis, or ≥50% reduction in eGFR.[7] Although the heart failure subgroup was too small to examine outcomes, the incidence of renal injury−related adverse events in the veverimer versus placebo group

appeared to be similar to that of the overall study population.

Metabolic acidosis may contribute to reduced exercise capacity in patients with heart failure and metabolic acidosis because of muscle loss from the catabolic effect of acidosis.[S2] In the overall study population, patient-reported limitations with daily activities such as walking and climbing a flight of stairs, as well as objective physical performance on the repeat chair stand test, improved during 1 year of veverimer treatment; these outcomes were unaffected by heart failure status.

The strengths of our study include the multicenter, randomized, blinded, placebo-controlled design, the rigor of evaluation of both serum bicarbonate and physical function endpoints, kidney injury events, and the 1-year treatment duration. The primary limitation was that that analysis was conducted *post hoc* in a subgroup of patients, and the results should be viewed as hypothesis generating. Subgroup inclusion was based on a reported diagnosis of heart failure, and heart failure adverse events were not adjudicated.

In conclusion, veverimer, an investigational, oral, non-absorbed polymer, increased serum bicarbonate in patients with heart failure and CKD-induced metabolic acidosis. There were no adverse effects of veverimer on volume status or blood pressure.

DISCLOSURE

VM, EL, and DAB were paid consultants to Tricida, Inc. in connection with the development of this manuscript. VM is a member of advisory boards at Tricida, listed on patents related to work for Tricida, and reports stock or stock options in Tricida. VM reports additional consulting fees from Tricida, Equillium, Myovant, Rigel, Corvidia, Acuta, Frazier, Intarcia, PTC Bio, and Sanifit outside the submitted work. DAB is a member of advisory board at Tricida and reports consulting fees, stock, and stock options from Tricida during and outside this work. DAB was the lead investigator for the phase 1/2 study of veverimer (TRCA-101) sponsored by Tricida and is on the advisory board for the ongoing VALOR-CKD post-marketing study sponsored by Tricida. DAB also reports consulting fees from Amgen, Sanofi/Genzyme, Fresenius/Relypsa/Vifor, personal fees as a medical advisory board member from Sanifit, speaker fees from Sanofi/Genzyme, and stock ownership in Amgen and past stock ownership in Relypsa, all outside this work. DAB reports grant support from the National Institutes of Health and Renal Research Institute, both outside this work.

ACKNOWLEDGMENTS

This study was funded by Tricida, Inc. The authors would like to thank Dawn Parsell and Jun Shao (both employees of Tricida) for review of the manuscript and help with the design of figures. Editorial support was provided by Jun Shao and Kathryn Boorer. Portions of this study were presented as an abstract at ASN Kidney Week 2020 Virtual Meeting, October 22–25, 2020, and at the National Kidney Foundation 2020 meeting (*Am J Kidney Dis.* 2020;75:653–654).

ClinicalTrials.gov Identifier: NCT03390842.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary Background

Supplementary Methods

Supplementary Results

Table S1. Kidney Disease and Quality of Life—Physical Functioning Domain

Table S2. Baseline characteristics

Figure S1. Study design.

Figure S2. Participant flow for heart failure subgroup.

Figure S3. Systolic and diastolic blood pressure over time.

Figure S4. Body weight over time.

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