RESEARCH LETTER

Effects of Veverimer in Older Adults With CKD and Metabolic Acidosis

To the Editor:

Chronic kidney disease (CKD) accelerates age-related decline in physical function. Metabolic acidosis, a common complication of CKD, leads to bone demineralization and muscle catabolism, and may contribute to frailty and sarcopenia in older adults.

Veverimer is an investigational, orally administered, nonabsorbed polymer that selectively binds and removes hydrochloric acid from the gastrointestinal tract, leading to increased serum bicarbonate.[1] Veverimer removes accumulated acid and, unlike exchange resins, does not deliver a counterion such as sodium or potassium.[1] In randomized, blinded, placebo-controlled trials in patients with CKD and metabolic acidosis, veverimer significantly increased serum bicarbonate within 1 week, with sustained effects through 1 year of treatment, and improved physical function.[1,2] No veverimer-drug interactions have been observed in human and in vitro studies.[3]

Here, we report the results of a post hoc analysis of the subgroup of patients ≥65 years old with metabolic acidosis (serum bicarbonate 12-20 mEq/L) and CKD (estimated glomerular filtration rate 20-40 mL/min/1.73 m^2) enrolled in a blinded, placebo-controlled, 40-week extension study (n = 196).[2] Complete methods have been reported.[1,2] In brief, patients were randomized 4:3 to once-daily veverimer or placebo in the 12-week parent study,[1] and blinded treatment was continued in the extension study.[2] Patients receiving stable doses of oral alkali supplements could be enrolled. The study protocol was approved by each site's relevant institutional review board or ethics committee and appropriate competent authorities in accordance with applicable laws and regulations. All participants gave their written informed consent to study participation.

We evaluated patient-reported limitations on the Kidney Disease and Quality of Life Physical Function Domain (KDQOL-PFD), a 10-item subscale that evaluates daily activities, including walking 1 or several blocks, climbing a flight of stairs, and lifting/bending/stooping. Physical performance was objectively measured on the standardized 5-times repeated chair stand (RCS) time.

To control family-wise error rate, hypothesis testing for the 4 efficacy end points was prespecified to be done sequentially, with subsequent tests only done when all previous tests were statistically significant at the 2-sided 0.05 level in both the parent study and the extension study. The Fisher exact test was used to compare the difference in group proportions at weeks 12 and 52. Change from baseline to weeks 12 and 52 in serum bicarbonate was analyzed using a mixed model for repeated measurements. Change from baseline to week 52 in the total score of the KDQOL-PFD and duration of the RCS test were analyzed using a rank-based analysis of covariance model.

Of the 196 enrolled patients, 96 (49%) were ≥65 years old; mean (standard deviation [SD]) age was 72 (4.9) years. Comorbid conditions included hypertension (98%), diabetes (70%), and congestive heart failure (40%). The mean (SD) baseline estimated glomerular filtration rate was 30.7 (6.1) mL/min/1.73 m^2 and mean (SD) serum bicarbonate was 17.2 (1.5) mEq/L. Baseline characteristics were generally similar between treatment arms (Table 1).

A higher proportion of patients ≥65 years receiving veverimer versus placebo met the primary study end point, defined as achievement of a ≥4 mEq/L increase in serum bicarbonate or normalization of serum bicarbonate at week 12 (79% vs 24%, $P < 0.001$); this effect was sustained at week 52 (69% vs 39%, $P = 0.005$) (Table 2). The week-12 least squares mean (LSM [standard error]) increase in serum bicarbonate was higher in the veverimer group (5.7 [0.38] mEq/L) than the placebo group (2.2 [0.48], $P < 0.001$). The increase in serum

Table 1. Baseline Characteristics of Patients ≥65 Years Old

	Veverimer (N = 58)	Placebo (N = 38)
Age (years), mean (SD)	72.1 (4.5)	71.6 (5.5)
Age ≥75 years, n (%)	17 (29%)	12 (32%)
Female, n (%)	25 (43%)	17 (45%)
Body mass index (kg/m^2), mean (SD)	29.0 (4.4)	27.4 (3.2)
Hypertension, n (%)	58 (100%)	36 (95%)
Diabetes, n (%)	41 (71%)	26 (68%)
Left ventricular hypertrophy, n (%)	39 (67%)	20 (53%)
Congestive heart failure, n (%)	24 (41%)	14 (37%)
Percutaneous coronary intervention or coronary artery bypass, n (%)	16 (28%)	9 (24%)
Myocardial infarction, n (%)	13 (22%)	8 (21%)
Stroke, n (%)	5 (9%)	4 (11%)
Peripheral vascular disease, n (%)	4 (7%)	4 (11%)
Serum bicarbonate (mEq/L), mean (SD)	17.4 (1.4)	16.9 (1.6)
eGFR (mL/min/1.73 m^2), mean (SD)	31.3 (6.5)	29.8 (5.4)
Hemoglobin (g/dL), mean (SD)	12.4 (1.7)	12.4 (1.7)
ACE inhibitor or ARB, n (%)	39 (68%)	31 (82%)
Previous oral alkali therapy, n (%)	5 (9%)	2 (5%)
KDQOL-PFD score (total score), mean (SD)	51.6 (20.3)	54.2 (23.5)
Repeated chair stand time (sec), mean (SD)	24.1 (16.2)	24.0 (18.6)

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; KDQOL-PFD, Kidney Disease and Quality of Life Physical Function Domain; SD, standard deviation.

Table 2. Study Results

	Veverimer	Placebo	Treatment Difference
Serum bicarbonate end points			
Primary: Proportion of patients achieving a serum bicarbonate increase of ≥4 mEq/L or normalization of serum bicarbonate at week 12, n/N (%)	46/58 (79%)	9/38 (24%)	*56% (95% CI: 37%, 71%)* *P* < 0.001
Secondary: Proportion of patients achieving a serum bicarbonate increase of ≥4 mEq/L or normalization of serum bicarbonate at week 52, n/N (%)	38/55 (69%)	14/36 (39%)	*30% (95% CI: 9%, 49%)* *P* = 0.005
Secondary: Change from baseline in serum bicarbonate at week 12 (mEq/L), LSM (SE)	5.7 (0.4) (N = 58)	2.2 (0.5) (N = 38)	*3.5 (95% CI: 2.3, 4.7)* *P*<0.001
Secondary: Change from baseline in serum bicarbonate at week 52 (mEq/L), LSM (SE)	5.4 (0.4) (N = 55)	2.4 (0.5) (N = 36)	*3.1 (95% CI: 1.7, 4.4)* *P* < 0.001
Physical function end points[a]			
Secondary: Change from baseline in KDQOL-PFD total score at week 52, median (95% CI of median[b])	10.0 (0.0 to 15.0) (N = 58)	0 (–5.0 to 0.0) (N = 38)	*10 (95% CI: 5, 20)* *P* = 0.003
Secondary: Change from baseline in 5-times repeated chair stand time at week 52 (s), median (95% CI of median[b])	–1.14 (–42.7 to 12.5) (N = 57)	+0.64 (–48.9 to 19.8) (N = 38)	*-1.78 (95% CI: -3.26, -0.51)* *P* = 0.003
Safety: Proportion of patients reporting the following events, n/N (%)			
Fatal adverse events	0/58	0/38	0
Adverse events leading to treatment discontinuation	0/58	0/38	0
Serious adverse event	1/58 (2%)	1/38 (3%)	*-1% (95% CI: -21%, 20%)*
Treatment-related adverse events	8/58 (14%)	7/38 (18%)	*-5% (95% CI: -25%, 16%)*
Gastrointestinal disorders adverse events	15/58 (26%)	14/38 (37%)	*-11% (95% CI: -31%, 10%)*

The 95% CI of difference in group proportions are based on the exact confidence limits.
Abbreviations: KDQOL-PFD, Kidney Disease and Quality of Life Physical Function Domain; LSM, least squares mean; SE, standard error.
[a]*P* values of the difference between the veverimer and placebo groups were based on the analysis of covariance model with the rank of change from baseline as the dependent variable, treatment as a fixed effect, baseline value, baseline estimated glomerular filtration rate, and baseline bicarbonate as continuous covariates.
[b]The 95% CI of difference in group medians is from Hodges-Lehmann estimator of location shift.

bicarbonate was maintained through week 52 (5.4 [0.44] vs 2.4 [0.54], $P < 0.001$).

Patients receiving veverimer reported fewer limitations with daily activities on the KDQOL-PFD, with a total score median increase of 10.0 versus no improvement in the placebo group ($P = 0.003$) at week 52. These differences exceeded the minimal clinically important difference of KDQOL subscales (3-5 points)[2] and were accompanied by significantly greater improvements in the RCS time in the veverimer group ($P = 0.003$) (Table 2).

Adherence, defined as consumption of >80% of doses, was achieved by all patients in both treatment groups.[2] Among patients ≥65 years old, there were no deaths and no adverse events leading to study drug discontinuation over 1 year of treatment. The incidence of serious adverse events, treatment-related adverse events, and gastrointestinal adverse events were all numerically lower in the veverimer group versus the placebo group (Table 2). Owing to limitations inherent in subgroup analyses, the results should be considered hypothesis generating.

To our knowledge, only 2 other randomized, placebo-controlled trials have evaluated the effects of treating metabolic acidosis on physical function.[4,5] Both were blinded and included the RCS test as an outcome measure and sodium bicarbonate as the intervention. Neither the physical function nor the quality-of-life end points were met in these studies.

The combined effects of aging and metabolic acidosis on sarcopenia and bone loss are of concern, as development of frailty is associated with morbidity and premature death. Additionally, ability to rise from a chair and perform activities, such as walking and stair-climbing, can adversely affect independence and quality of life. We found that treatment of metabolic acidosis with veverimer in older adults with CKD improved how patients felt and functioned and has the potential to reduce disability related to declining physical function.

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