Sucroferric Oxyhydroxide as Part of Combination Phosphate Binder Therapy among Hemodialysis Patients

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Abstract

Background Combination therapy with multiple phosphate binders is prescribed to reduce elevated serum phosphorus (sP) concentrations among patients on maintenance hemodialysis. Sucroferric oxyhydroxide (SO), an iron-based phosphate binder, has demonstrated efficacy at reducing sP while also being associated with a low pill burden. Whereas the effects of SO monotherapy have been well characterized in clinical trials and observational cohorts, little is known about the effects of SO-containing combination therapy.

Methods Patients on hemodialysis (N=234) at Fresenius Kidney Care (FKC) who received ≥120 days of uninterrupted phosphate binder combination therapy with SO were included in this retrospective study. Patient data were censored after SO discontinuation, end of care at FKC, or completion of 12 months of follow-up. Quarterly (Q) changes in phosphate binder pill burden, mean sP, and proportion of patients achieving National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI)–recommended sP levels (≤5.5 mg/dl) were compared between baseline (–Q1) and follow-up (Q1–Q4).

Results Phosphate binder combination therapy with SO was associated with significant increase in the proportion of patients with sP ≤5.5 mg/dl (from 19% at baseline to up to 40% at follow-up; P<0.001) and reduction in sP at all postbaseline time points (from 6.7 mg/dl to 6.2–6.3 mg/dl; P<0.001). Patients on calcium acetate (N=54) and sevelamer (N=94) who added SO therapy at follow-up resulted in a ≥250% increase in patients achieving sP ≤5.5 mg/dl (all P<0.001). Whereas mean phosphate binder pill burden increased with initiation of phosphate binder combination therapy with SO (15.8 pills/d at Q1 versus 12.3 pills/d at –Q1), continued use of SO was associated with down-titration of non-SO phosphate binders such that, by Q4, mean total PB pill burden reduced to 12.3 pills/d.

Conclusions For patients on hemodialysis with uncontrolled hyperphosphatemia, combination therapy with SO may allow for sustained improvements in sP control without adversely affecting phosphate binder pill burden.

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Introduction

CKD is associated with disturbances in phosphorus homeostasis. In early stages of disease, compensatory mechanisms can maintain physiologic phosphorus levels (1,2). Compensatory mechanisms include increases in phosphatins such as fibroblast growth factor-23 that directly reduce renal phosphate reabsorption and also result in reductions in active vitamin D; the latter reduces phosphorus absorption from the gastrointestinal tract and tubular reabsorption of filtered phosphorus by the kidney (3,4). As kidney function declines and compensatory mechanisms—in particular renal excretion of phosphorus—are significantly impaired, overt hyperphosphatemia can develop and is often evident in later stages of CKD (i.e., stages 4 and 5) (5). High serum phosphorus (sP) levels have been associated with adverse outcomes in the setting of ESKD, including increased risk of cardiovascular events and reduced survival, particularly among populations on hemodialysis (HD) (6–10).

Prospective observational data collected as part of COSMOS (the Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study) support efforts to lower elevated sP concentrations in patients on HD (11). In COSMOS, a survival benefit was observed among patients on HD with elevated baseline sP levels (i.e., >5.2 mg/dl [mean, 6.5 mg/dl]) who demonstrated reductions in sP concentrations during follow-up. Strategies to lower sP in patients on HD include restriction of dietary phosphate while ensuring adequate intake of protein and avoidance of malnutrition (12,13), adjustments in the HD prescription (12,14), and pharmacotherapy with phosphate binders (PBs) to reduce intestinal phosphate absorption (2).

National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommend maintenance of sP between 3.5 and 5.5 mg/dl in patients on dialysis (15). Because of a lack of data from randomized controlled trials, recommendations regarding specific

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clinical approaches are largely absent from the guidelines. Observational studies, however, demonstrate that prescribed PB therapy is associated with a survival benefit among patients on HD (16–18). Presently, more than three quarters of patients on HD in the United States are prescribed PBs, but >40% have sP levels >5.5 mg/dl (19,20), and approximately 17% have sP concentrations >7.0 mg/dl (20).

According to Sekar et al. (21), PB selection should be individualized to the needs of the patient and should consider the patient’s metabolic profile (e.g., iron and calcium stores), safety, pill burden, and cost. Pill burden and its potential effect on adherence may be particularly relevant for patients on HD because of the high rates of polypharmacy in this population (22,23). Sucroferric oxyhydroxide (SO) is an effective, iron-based PB approved for the control of sP in patients with CKD on dialysis with demonstrated effectiveness at a lower pill burden in randomized controlled trials with SO monotherapy (24–29). The effectiveness of SO monotherapy has also been assessed in retrospective studies examining the “real-world” effects of starting, or switching to, SO therapy (30–32). In these analyses, improvements in sP, reductions in pill burden, and improved adherence have been reported.

Combination therapy with PBs is not currently addressed within evidence-based recommendations and the safety and efficacy of such dosing strategies have not been rigorously studied in clinical trials. Nonetheless, combination PB therapy is used in clinical practice and has been associated with a survival benefit in COSMOS (18,33,34). This retrospective analysis aimed to examine the effects of SO among patients on HD when prescribed with other PBs for up to 1 year.

Materials and Methods

Study Design

This retrospective cohort study used de-identified data extracted from the Fresenius pharmacy (FreseniusRx) database. All adult, in-center patients on HD prescribed SO in combination with other PBs for at least 120 days of therapy as part of routine care at Fresenius Kidney Care (FKC) facilities between April 1, 2014 and April 1, 2015 were included in this analysis (Figure 1). SO is an iron-based PB with a recommended starting dose of three pills per day (administered as one pill three times daily with meals) indicated for the control of sP in patients with CKD on dialysis.

Eligible non-SO PBs included calcium acetate, lanthanum carbonate, sevelamer carbonate, and sevelamer hydrochloride. Calcium carbonate as a PB was not included because we

Figure 1. | Patient disposition flow chart detailing patients in the overall study cohort (n=234) with subgroups and patients excluded from the overall study cohort but included in sensitivity analyses (n=222). *Reasons for discharge from Fresenius Kidney Care (FKC) included transplantation, transfer to non-FKC facilities, withdrawal from dialysis, or death. FreseniusRx, Fresenius specialty pharmacy; HD, hemodialysis; PB, phosphate binder; Q, quarter; SO, sucroferric oxyhydroxide.
were unable to track prescriptions as it is available over the counter. Treatment periods were defined quarterly (Q) as baseline (−Q1; 3 months before SO prescription) and follow-up (Q1 through Q4; up to 12 months of SO prescription; Figure 2). Treatment data were censored if (1) patients disenrolled from FreseniusRx, (2) SO therapy was discontinued, or (3) patients no longer received HD at FKC facilities (e.g., post-transplantation, transfer to other facilities, or death).

Clinical Variables and Statistical Analysis

Clinical and laboratory parameters of interest included prescribed PB pills per day (for SO and non-SO PBs); serum levels of phosphorus, calcium, and albumin; intact parathyroid hormone (iPTH); single-pool values of normalized protein catabolic rate and dialysis adequacy (i.e., Kt/V); and dose and use of active vitamin D and calcimimetic therapies. Mean clinical variables were summarized using least-squared means and compared between baseline and follow-up using repeated-measures mixed effects linear regression. Laboratory measures repeated over any quarter were averaged to account for short-term measurement variability. The proportion of patients within the upper limit of NFK-KDOQI–recommended sP (sP ≤5.5 mg/dl) was compared between baseline and follow-up. Categorical data were compared using the McNemar chi-squared and Cochran Q tests.

Analyses were carried out for all patients and the subgroup of patients who added SO therapy to their baseline PB regimen to examine changes in sP and daily PB pill burden overall and were stratified by baseline and follow-up using repeated-measures mixed effects linear regression. Laboratory measures repeated over any quarter were averaged to account for short-term measurement variability. The proportion of patients within the upper limit of NFK-KDOQI–recommended sP (sP ≤5.5 mg/dl) was compared between baseline and follow-up. Categorical data were compared using the McNemar chi-squared and Cochran Q tests.

Analyses were carried out for all patients and the subgroup of patients who added SO therapy to their baseline PB regimen to examine changes in sP and daily PB pill burden overall and were stratified by baseline PB regimen. Two sensitivity analyses were conducted. The first addressed the effect of loss to follow-up on study results by examining subgroups of patients who completed SO treatment through Q4 (completers) and patients who discontinued SO therapy during follow-up (noncompleters). The second sensitivity analysis was conducted to assess the degree of selection bias introduced by the requirement of 120 days of prescription of SO in combination with other PBs between April 1, 2014 and April 1, 2015; 234 individuals met the study criteria and were included in the analysis (Figure 1). Patients had a mean age of 52 years and had been receiving HD treatment for approximately 4.6 years (Table 1). Before the initiation of SO, mean (SD) sP was 6.7 (1.4) mg/dl (range, 3.43–11.13 mg/dl). The most common baseline PB was sevelamer carbonate, and approximately one quarter of patients were on combination PB therapy at baseline (i.e., before starting SO). Table 2 details the PB therapies received by all patients at baseline and in combination with SO at follow-up.

Treatment with SO was associated with significant reductions in sP at all postbaseline time points from baseline (Figure 3, Table 3). There were significant increases in the proportion of individuals with an sP ≤5.5 mg/dl (19% at baseline to 33%–40% at follow-up; P <0.001). The total PB pill burden increased from 12.3±6.4 pills per day at −Q1 to 15.8±5.7 pills per day at Q1 (P <0.001) with the addition of SO treatment, but the non-SO PB pill burden was down-titrated over time such that, by Q4, mean total PB pill burden was 12.3±5.1 pills per day (−Q1 versus Q4, P =0.9). Mean non-SO PB pill burden was reduced by approximately 19% from 12.3±6.4 pills per day at −Q1 to 10.0±4.9 pills per day at Q4 (P =0.05).

Small decreases in serum albumin (4.0 mg/dl at −Q1, and 3.95, 3.97, 3.98, and 3.96 mg/dl at Q1, Q2, Q3, and Q4, respectively; P =0.001), and no significant changes in single-pool Kt/V or normalized protein catabolic rate were observed (Table 3). Minor decreases in serum calcium concentrations (2%) and increases in intact PTH (9%) were observed during follow-up (Table 3). The proportions of patients who received

**Results**

**Overall Study Cohort (N=234)**

Out of 456 adult, in-center patients on HD at FKC facilities who received one or more prescriptions of SO in combination with other PBs between April 1, 2014 and April 1, 2015; 234 individuals met the study criteria and were included in the analysis (Figure 1). Patients had a mean age of 52 years and had been receiving HD treatment for approximately 4.6 years (Table 1). Before the initiation of SO, mean (SD) sP was 6.7 (1.4) mg/dl (range, 3.43–11.13 mg/dl). The most common baseline PB was sevelamer carbonate, and approximately one quarter of patients were on combination PB therapy at baseline (i.e., before starting SO). Table 2 details the PB therapies received by all patients at baseline and in combination with SO at follow-up.

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Small decreases in serum albumin (4.0 mg/dl at −Q1, and 3.95, 3.97, 3.98, and 3.96 mg/dl at Q1, Q2, Q3, and Q4, respectively; P =0.001), and no significant changes in single-pool Kt/V or normalized protein catabolic rate were observed (Table 3). Minor decreases in serum calcium concentrations (2%) and increases in intact PTH (9%) were observed during follow-up (Table 3). The proportions of patients who received

**Figure 2.** Study design including a three-month baseline and 12-month follow-up, analyzed quarterly (Q1 to Q4) and monthly. *Reasons for discharge from FKC includes transplantation, transfer to non-FKC facilities, withdrawal from dialysis, or death.
oral vitamin D and cinacalcet therapies increased over follow-up, whereas there was a slight decrease in the use of intravenous vitamin D (Supplemental Table 1).

**Subgroup Analysis of Patients Who Added SO Therapy to Baseline PB Therapy (N=196)**

At baseline, SO was added to the existing PB for 84% (N=196) of the cohort; subgroup analyses were performed on this population (Table 4). Significant reductions in mean sP and improvements in patients achieving an sP $\leq$5.5 mg/dl were observed independent of PB combinations. Patients who added SO to baseline calcium acetate therapy (N=54) achieved a greater than trifold increase in sP control (sP $\leq$5.5 mg/dl; 13% at $-$Q1 to 30% at Q4; $P<0.001$) and mean total PB pill burden increased from 10.2 calcium acetate pills per day at baseline to 11.2–13.7 (calcium acetate+SO) pills per day at follow-up ($P<0.001$). There were no significant changes observed in serum calcium (9.1 mg/dl at $-Q1$ to 9.0 mg/dl at Q4; $P=0.06$) and intact PTH (502 pg/ml at $-Q1$ to 569 pg/ml at Q4; $P=0.24$). Among the 94 patients who added SO to baseline sevelamer therapy, there were significant improvements in rates of achievement of sP $\leq$5.5 mg/dl (18% at baseline to up to 45% at follow-up; $P<0.001$) and significant reduction in mean sP ($\Delta = -0.5$ mg/dl; $P<0.001$). With the addition of SO to existing sevelamer therapy, mean total PB pill burden increased from 11.5 pills per day at $-Q1$ to 15.7 pills per day at Q1, but was significantly titrated down over time (12.8 pills per day at Q4). There were statistically significant decreases in mean serum calcium (9.2 mg/dl at $-Q1$ to 9.0 mg/dl at Q4; $P<0.001$) and increases in mean intact PTH (587 pg/ml at $-Q1$ to 631 pg/ml at Q4; $P<0.001$). Similarly, patients on other PB combinations who added SO to their baseline PB treatment regimens (N=48) had significant reductions in mean sP and serum calcium and increases in patients achieving sP $\leq$5.5 mg/dl, mean total PB pill burden, and intact PTH levels.

**Subgroup Analysis of Completers (N=134) and Noncompleters (N=100)**

A sensitivity analysis of patients who completed SO therapy through Q4 (completers) and patients who discontinued SO before Q4 (noncompleters) was conducted to address the potential for bias from loss to follow-up. S’ decreased significantly from baseline (6.8 mg/dl in completers, 6.6 mg/dl in noncompleters) to follow-up (6.2–6.3 mg/dl in both groups; $P<0.001$), a mean decrease of $-0.46$ mg/dl and $-0.38$ mg/dl, respectively (Table 5). Proportions of individuals achieving an sP of $\leq$5.5 mg/dl improved significantly in both completers (+135%) and noncompleters (+76%). Among completers, although total PB pill burden increased from baseline to Q1 with the addition of SO, non-SO PB pill burden was decreased by 1.2 mg/dl (Q4).

### Table 1. Demographic characteristics of the study cohort (N=234)

| Measure                                      | Study Cohort               |
|----------------------------------------------|----------------------------|
| Age, yr                                      | 51.8±13.4                  |
| Dialysis vintage, mo                        | 55.0±45.6                  |
| Female, n (%)                               | 98 (42)                    |
| Body mass index, kg/m²                      | 33.1±8.9                   |
| Hemodialysis treatment time per week, h     | 10.7±1.6                   |
| Race/ethnicity, n (%)                       |                            |
| White                                        | 123 (53)                   |
| Black                                        | 92 (39)                    |
| Hispanic/Latino                             | 36 (15)                    |
| Comorbidities, n (%)                        |                            |
| Diabetes mellitus                           | 138 (59)                   |
| Congestive heart failure                    | 69 (30)                    |
| Charlson Comorbidity Index                  | 4.7±2.0                    |
| Baseline phosphate binder, n (%)            |                            |
| Sevelamer                                    | 96 (41)                    |
| Calcium acetate                             | 59 (25)                    |
| Lanthanum carbonate                         | 7 (3)                      |
| PB polytherapya                             | 56 (24)                    |
| No PB recorded                              | 16 (7)                     |
| Clinical laboratory measures at baseline    |                            |
| Serum phosphorus, mg/dl                     | 6.7±1.4                    |
| Serum calcium, mg/dl                        | 9.1±0.6                    |
| Intact PTH, pg/ml                           | 572±493                    |
| Serum albumin, g/dl                         | 4.0±0.3                    |
| Single-pool Kt/V                            | 1.7±0.1                    |

Data are presented as mean±SD, or n (%). PB, phosphate binder; PTH, parathyroid hormone; CaAc, calcium acetate; Sev, sevelamer carbonate; LC, lanthanum carbonate.

### Table 2. Follow-up phosphate binder therapy combinations with sucroferric oxyhydroxide by baseline phosphate binder (N=234)

| Baseline PBb | PB Therapy Combinations at Follow-Up |
|--------------|--------------------------------------|
|              | CaAc+SO | LC+SO | Sev+SO | CaAc+Sev+SO | CaAc+LC+SO | Sev+LC+SO | CaAc+Sev+LC+SO |
| No PB recorded | 4 (2)   | 1 (0.4) | 11 (5) | 0         | 0    | 0     | 0     |
| CaAc          | 54 (23) | 0      | 0      | 11 (5)    | 0    | 0     | 0     |
| LC            | 0       | 5 (2)  | 0      | 0         | 0    | 0     | 0     |
| Sev           | 0       | 0      | 94 (40) | 2 (0.9)  | 0    | 0     | 0     |
| CaAc+Sev      | 0       | 0      | 0      | 3 (1)     | 0    | 0     | 2 (0.8)b  |
| CaAc+LC       | 0       | 0      | 0      | 0         | 7 (3) | 0     | 0     |
| Sev+LC        | 0       | 0      | 3 (1)  | 0         | 0    | 6 (3) | 0     |

Data are presented as n (%). PB, phosphate binder; CaAc, calcium acetate; SO, sucroferric oxyhydroxide; LC, lanthanum carbonate; Sev, sevelamer carbonate.

bAt baseline, if multiple PB therapies were recorded, the last combination before SO initiation was included in the table.

bPatients received LC prescription for <30 d.
down-titrated over time such that, by Q4, there was no significant increase in number of pills from Q1 ($P=0.38$). In contrast, there was a consistent increase in total PB pill burden from baseline among noncompleters during all postbaseline time points (Q1–Q4), including treatment quarters post-SO discontinuation.

**Comparison of Patients Included versus Excluded from Overall Study Cohort**

A sensitivity analysis was conducted to assess the degree of selection bias introduced by the requirement of 120 days of prescription of SO in combination with other PBs (Figure 1). A comparison of 222 patients on HD who received ≥120 days of prescription of SO in combination with other PBs at FK3 facilities was made with patients who completed the 120 days ($n=234$). More specifically, monthly mean sP during baseline (months $-3$, $-2$, and $-1$) and the first 120 days of follow-up (months +1, +2, +3, and +4) were evaluated. Before the initiation of SO therapy, mean sP was 6.8 mg/dL, which was similar to the mean sP observed among patients in the study cohort (mean sP=6.79 mg/dL; Supplemental Table 2). Post-baseline sP levels decreased from 6.39 mg/dL at month +1 to 6.30 mg/dL at month +4, a mean decrease of $-0.45$ mg/dL from baseline. Patients included in the study cohort experienced a decrease in mean sP from 6.36 mg/dL at month +1 to 6.13 mg/dL at month +4, a mean decrease of $-0.51$ mg/dL from baseline.

**Discussion**

In this retrospective cohort study, patients on HD initiating SO in combination with another PB demonstrated significant reductions in sP. Such reductions were observed across a spectrum of SO-containing PB regimens and were maintained for the duration of SO therapy (up to 1 year). Although >90% of patients were already being treated with at least one PB and nearly one quarter were receiving combination therapy at baseline, the cohort exhibited marked hyperphosphatemia (mean sP=6.7 mg/dL) before SO was prescribed (i.e., at baseline). After 1 year of PB therapy including SO, 37% of patients attained an sP of $\leq 5.5$ mg/dL. Because SO therapy was often prescribed as add-on therapy to other PBs, it is not surprising that patients experienced an initial increase in pill burden. Continuation of SO therapy allowed for a decrease in total PB pill burden over time, suggesting that clinicians down-titrated the dose of other PBs (or discontinued other PBs) while up-titrating the dose of SO (Table 3).
Table 3. Longitudinal changes in clinical and laboratory parameters from baseline to follow-up (N=234)

| Treatment Period | Mean PB Pill Burden (pills/d) | Serum Phosphorus (mg/dl) | Mean | sP ≤5.5 mg/dl (%) | Serum Calcium (mg/dl) | Intact PTH (pg/ml) | Serum Albumin (g/dl) | nPCR (g/kg per d) | Single-Pool Kt/V |
|------------------|-------------------------------|--------------------------|------|------------------|-----------------------|-------------------|-------------------|-----------------|-----------------|
|                  | All PB | SO | Non-SO PB | Mean | sP ≤5.5 mg/dl (%) | Serum Calcium (mg/dl) | Intact PTH (pg/ml) | Serum Albumin (g/dl) | nPCR (g/kg per d) | Single-Pool Kt/V |
| Baseline         |        |    |           | Mean | sP ≤5.5 mg/dl (%) | Serum Calcium (mg/dl) | Intact PTH (pg/ml) | Serum Albumin (g/dl) | nPCR (g/kg per d) | Single-Pool Kt/V |
| –Q1 (referent) (N=234) | 12.3 | N/A (by design) | 12.3 | 6.72 | 45/234 (19)      | 9.15               | 584               | 4.0              | 1.06            | 1.71            |
| Follow-up        |        |    |           | Mean | sP ≤5.5 mg/dl (%) | Serum Calcium (mg/dl) | Intact PTH (pg/ml) | Serum Albumin (g/dl) | nPCR (g/kg per d) | Single-Pool Kt/V |
| Q1 (N=234)       | 15.8d  | 4.0 | 11.8d     | 6.32d | 78/234 (33)d | 9.10e             | 568               | 3.97e            | 1.05            | 1.73            |
| Q2 (N=234)       | 15.5d  | 4.2 | 11.3d     | 6.17d | 93/233 (40)d | 9.09e             | 565               | 3.97e            | 1.06            | 1.72            |
| Q3 (N=202)       | 13.6d  | 4.3 | 10.6d     | 6.23d | 64/185 (35)d | 9.02d             | 629               | 3.98d            | 1.04            | 1.70            |
| Q4 (N=134)       | 12.3   | 4.6 | 10.0f     | 6.25d | 46/125 (37)d | 8.99d             | 634               | 3.96e            | 1.01            | 1.68            |
| P valueg         | <0.001 | N/A | <0.001    | <0.001 | <0.001 | <0.001 | 0.006 | 0.001 | 0.05 | 0.5 |

Data are presented as least-squared means or n/N (%). PB, phosphate binder; SO, sucroferric oxyhydroxide; sP, serum phosphorus; PTH, parathyroid hormone; nPCR, normalized protein catabolic rate; Q, quarter; N/A, not applicable; FreseniusRx, Fresenius specialty pharmacy; HD, hemodialysis; FKC, Fresenius Kidney Care.

aNon-SO PB therapies included calcium acetate, lanthanum carbonate, and sevelamer.
bPatients with missing sP were not included in the denominator N.
cStatistical comparisons were not carried out because patients initiated SO therapy only at follow-up.
dp<0.001.
ep<0.05.
fMean non-SO PB pill burden during treatment with PB combination therapy with SO. Data were censored when SO prescription ended, patients disenrolled from FreseniusRx, or when patients stopped receiving HD treatment at FKC.
gP values compare summary measures with –Q1 as the referent.
Whereas combination therapy with PBs has been previously reported, we could identify only one other study specifically designed to examine SO as a component of PB combination therapy (33). In that 12-week exploratory study, 35 adult patients on HD with sP between 3.5 and 6.0 mg/dl maintained on calcium carbonate plus sevelamer hydrochloride were switched to calcium carbonate plus SO. SO was administered three times daily at total daily doses of 750–3000 mg and calcium carbonate doses were to be held constant. Investigators found that, while simultaneously reducing pill burden, sP concentrations were maintained constant. Investigators found that, while simultaneously

| Patients Who Added SO to their Baseline PB | n | Baseline –Q1 (referent) | Follow-Up Q1 | Q2 | Q3 | Q4 | P Valuea |
|-----------------------------------------|---|------------------------|-------------|----|----|----|----------|
| Serum phosphorus (mg/dl)                |   |                        |             |    |    |    |          |
| All patients                            | 196| 6.73                   | 6.31b       | 6.17b | 6.22b | 6.25b | <0.001   |
| (Sev) to (Sev+SO)                       | 94 | 6.80                   | 6.33b       | 6.08b | 6.26b | 6.26b | <0.001   |
| (CaAc) to (CaAc+SO)                     | 54 | 6.55                   | 6.26c       | 6.05b | 6.03b | 6.24  | 0.002    |
| Otherb                                 | 48 | 6.80                   | 6.33b       | 6.46c | 6.32c | 6.27b | <0.001   |
| sP ≤5.5 mg/dl (%)                       |   |                        |             |    |    |    |          |
| All patients                            | 196| 18                     | 34b         | 40b  | 37b  | 37b  | <0.001   |
| (Sev) to (Sev+SO)                       | 94 | 18                     | 35b         | 45b  | 35   | 33   | 0.007    |
| (CaAc) to (CaAc+SO)                     | 54 | 13                     | 32          | 43b  | 44b  | 50b  | 0.004    |
| Otherb                                 | 48 | 25                     | 33          | 27   | 34   | 34   | 0.92     |
| Total PB pill burden (pills/d)          |   |                        |             |    |    |    |          |
| All patients                            | 196| 12.1                   | 15.9b       | 15.8b | 13.9b | 12.7c | <0.001   |
| (Sev) to (Sev+SO)                       | 94 | 11.5                   | 15.7b       | 16.0b | 14.1b | 12.8b | <0.001   |
| (CaAc) to (CaAc+SO)                     | 54 | 10.2                   | 13.7b       | 13.8b | 12.1b | 11.2  | <0.001   |
| Otherb                                 | 48 | 15.3                   | 18.8b       | 17.5b | 15.7 | 14.3c | <0.001   |
| SO pill burden (pills/d)                 |   |                        |             |    |    |    |          |
| All patients                            | 196| N/A (by design)        | 4.0         | 4.2  | 4.3  | 4.6  | N/A      |
| (Sev) to (Sev+SO)                       | 94 | 4.0                    | 4.0         | 4.5  | 4.7  |       |          |
| (CaAc) to (CaAc+SO)                     | 54 | 3.8                    | 3.9         | 4.0  | 4.3  |       |          |
| Otherb                                 | 48 | 4.2                    | 4.4         | 4.4  | 4.6  |       |          |

Data are presented as least-squared means or percentages. SO, sucroferric oxyhydroxide; PB, phosphate binder; Q, quarter; Sev, sevelamer; CaAc, calcium acetate; sP, serum phosphorus; LC, lanthanum carbonate.

aP values compare summary measures with –Q1 as the referent.
bP<0.01.

cP<0.05.

dOther PB combinations include patients who switched from LC to (LC+SO), (Sev+CaAc) to (Sev+CaAc+SO), (LC+CaAc) to (LC+CaAc+SO), and (Sev+LC) to (Sev+LC+SO).

eStatistical comparisons were not carried out because patients initiated SO therapy only at follow-up.

Nonadherence to prescribed PB regimens is common, with one study finding that only 43% of United States patients reported complete adherence in the prior month (36,37). Because pill burden has been associated with reduced adherence and reduced sP control, it is a relevant consideration in the management of hyperphosphatemia (23,37,38). In this study, combination PB therapy with SO, most often as an addition of SO to an existing PB regimen, resulted in an initial increase in pill burden. With continued SO use, however, PB pill burden was gradually reduced while significantly reduced sP levels were maintained.

This observational study presents data from the largest cohort of patients on HD prescribed combination PB therapy with SO reported to date. Beyond the observational nature of the study, the results should be considered in light of several limitations. We did not consider the dose of prescribed PBs or the frequency of administration in this analysis. It is possible that different PBs were being...
prescribed for administration at different times of the day (e.g., with meals versus with snacks) or being dosed variably throughout the day. The use of variable PB dosing informed by phosphate intake may help to compensate for variable dietary phosphate intake (39). Our study also used a single source of prescription data, so the possibility that medications were obtained through other pharmacy services or over the counter, as in the case of calcium carbonate, cannot be excluded. Prescription data, although informative, is not a surrogate for actual patient adherence with prescribed regimens. The reasons for discontinuation of SO therapy were not captured in our electronic health records database, but reasons may include lack of effectiveness, nonadherence to PB therapy regimen, insurance coverage, and out-of-pocket costs. Data on safety (e.g., adverse reactions) were not available in the clinical database. Lastly, we cannot draw any conclusions regarding SO treatment and effects on mortality, significant morbidities, or quality of life. Future studies should examine the effect on clinical outcomes such as hospital admissions or mortality and patient-centered outcomes such as quality of life.

We did not have access to data regarding the clinical rationale for PB initiation/discontinuation or dose adjustments which allows for the possibility of a selection bias. A conducted sensitivity analysis assessed selection bias due to early stopping of SO therapy before 120 days and found that, during SO treatment, included and excluded patients had similar decreases in sP. To assess potential differences between this study population and patients prescribed SO monotherapy, we examined a previously reported, real-world cohort of patients on HD prescribed SO monotherapy (Supplemental Table 3) (31). Relative to this study, patients switching from another PB to SO monotherapy had higher baseline sP, lower daily PB pill burden, and fewer comorbidities. These findings suggest that combination therapy with SO was initiated after baseline PB therapy had been up-titrated but that clinicians were still not satisfied with attained sP levels.

In this observational cohort study, SO was associated with significant improvement in sP when initiated as part of combination therapy for hyperphosphatemia. The findings support the use of SO in combination with other PBs to allow for a treatment regimen tailored to the needs of patients and clinicians.

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**Author Contributions**

All authors conceptualized the study, were responsible for investigation and methodology, and reviewed and edited the manuscript; L. Ficociello was responsible for project administration; L. Ficociello and V. Parameswaran were responsible for data curation, formal analysis, validation, and visualization; L. Ficociello, R. Kossmann, and D. Molony were responsible for supervision; and L. Ficociello, R. Kossmann, and C. Mullon were responsible for resources.

**Disclosures**

L. Ficociello, R. Kossmann, C. Mullon, and V. Parameswaran are employees of Fresenius Medical Care Renal Therapies Group. R.
Kossmann and C. Mullon own stock in Fresenius Medical Care North America. R. Kossmann is on the board of directors of Advanced Renal Technologies. D. Molony is professor of medicine at the McGovern Medical School, University of Texas Houston, and reports personal fees from Fresenius Medical Care outside the submitted work.

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**Supplemental Material**

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000332019/-/DSupplemental.

Supplemental Table 1. Longitudinal changes in prescription patterns of mineral bone disease medications (N=234).

Supplemental Table 2. Comparison of serum phosphorus levels between patients in the study cohort (N=234) and patients who stopped combination therapy with SO within 120 days of SO initiation (N=222).

Supplemental Table 3. Comparison of demographic characteristics between study cohort and a historic cohort of hemodialysis patients prescribed SO monotherapy.

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