Sucroferric Oxyhydroxide in Maintenance Hemodialysis: A Retrospective, Comparative Cohort Study

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Rationale & Objective: High pill burden associates with reduced phosphate-binder adherence among dialysis patients, contributing to elevated serum phosphorus levels. We compared the real-world effectiveness of sucroferric oxyhydroxide (SO) versus other phosphate binders in hemodialysis patients over 2 years.

Study Design: Retrospective cohort study.

Setting & Participants: Adult in-center hemodialysis patients prescribed 2 years of uninterrupted SO therapy (maintenance SO; n = 222) compared with patients who discontinued SO therapy (discontinued SO; n = 596) within 90 days of first prescription and switched to other phosphate binder(s) for 2 years.

Exposures: Phosphate binders.

Outcomes: Achievement of serum phosphorus levels ≤ 5.5 mg/dL, pill burden, and hospitalizations.

Analytical Approach: Comparisons were made quarterly (Q1-Q8) between maintenance SO and discontinued SO using Poisson and mixed-effects linear regression.

Results: Patients achieving serum phosphorus levels ≤ 5.5 mg/dL increased from baseline in maintenance SO (46 [20.7%] to a maximum of 104 [46.8%]; $P < 0.001$) and discontinued SO (96 [16.1%] to a maximum of 201 [33.7%]; $P < 0.001$). 100 (45%) maintenance SO patients achieved target serum phosphorus levels at Q8 with 3.1 fewer pills per day from baseline (7.5 to 4.4 pills per day; $P < 0.001$), and 190 (31.9%) discontinued SO patients achieved serum phosphorus levels ≤ 5.5 mg/dL at Q8 with pill burden unchanged (9.1 to 9.3 pills per day; $P = 0.3$). Among all patients during 2 years, mean serum phosphorus levels decreased by −0.66 mg/dL and −0.45 mg/dL (maintenance SO vs discontinued SO; $P = 0.014$), and mean pill burden decreased in maintenance SO (8.5 to 5.1 pills per day; $P < 0.001$), but not in discontinued SO (11.6 to 10.9 pills per day; $P = 0.2$). The serum phosphorus level decrease with SO was confirmed in a sensitivity analysis including patients with SO therapy for 2 or fewer years. Compared with discontinued SO, maintenance SO patients had 35.6 fewer hospitalizations per 100 patient-years (incidence rate ratio, 0.75 [95% CI, 0.58-0.96]).

Limitations: No data for treatment indication, tolerance, or adherence.

Conclusions: Patients maintained on SO therapy were more likely to achieve target serum phosphorus levels, use 50% fewer phosphate-binder pills per day, and have fewer hospital admissions than patients switched to treatment with other binders.

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Hyperphosphatemia is a consequence of end-stage kidney disease that occurs due to impaired renal phosphate excretion[1] and has been associated with increased cardiovascular morbidity and mortality.[2-5] In addition to undergoing dialysis and limiting dietary phosphorus intake, most patients with end-stage kidney disease require treatment with oral phosphate binders to control their serum phosphorus concentrations.[6,7] Despite the association between elevated serum phosphorus levels and adverse clinical outcomes, approximately 40% of US dialysis patients[8] have serum phosphorus concentrations above the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) recommended range (3.5-5.5 mg/dL).[9]

Many phosphate binders have a high pill burden, which has been linked to reduced treatment adherence and may contribute to inadequate serum phosphorus control.[10-13] Nonadherence to phosphate-binder therapy has been reported for more than half (57%) the US hemodialysis patients.[13] Availability of effective phosphate binders with lower pill burden may increase adherence and improve serum phosphorus control.

Sucroferric oxyhydroxide (SO; Velphoro; Fresenius Medical Care Renal Therapies Group) is an iron-based phosphate binder indicated for the treatment of hyperphosphatemia in maintenance dialysis patients. A phase 3 randomized clinical trial[14] demonstrated that SO had similar serum phosphorus-lowering efficacy to sevelamer carbonate, but a substantially lower mean pill burden (3.3 vs 8.7 pills per day, respectively) over a 1-year period.[15]

Previous 6- and 12-month retrospective database analyses of hemodialysis patients showed that switching to SO monotherapy, compared with their historic treatment with other phosphate binders, was associated with an approximate doubling in the proportion of patients achieving target serum phosphorus levels (≤5.5 mg/dL) while simultaneously reducing mean phosphate-binder pill burden by ≥50%.[16,17]

To address the potential weaknesses of previous studies conducted without a control group, we used a novel study

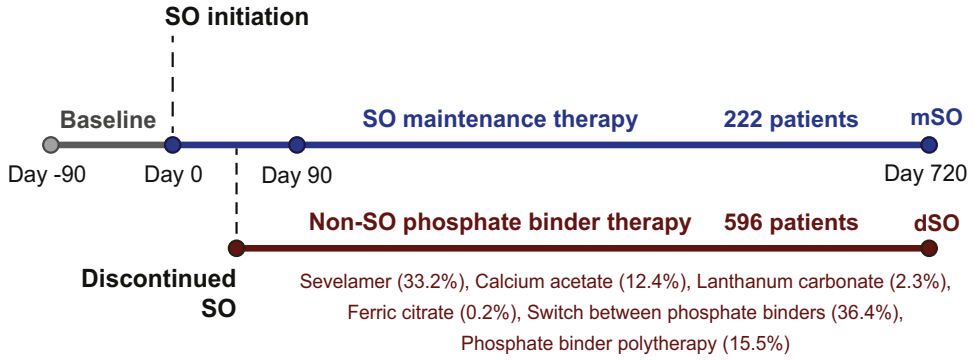

Figure 1. Study design. Abbreviations: dSO, patients who discontinued sucroferric oxyhydroxide therapy and were treated with non-sucroferric oxyhydroxide phosphate binder; mSO, patients who received 2 years of maintenance therapy with sucroferric oxyhydroxide; SO, sucroferric oxyhydroxide.

design. Patients maintained on SO therapy (maintenance SO) for 2 years were compared with an active control group of patients (discontinued SO) who discontinued SO therapy within 90 days and switched to other phosphate binder(s). We evaluated the achievement of target serum phosphorus levels (≤5.5 mg/dL), phosphate-binder pill burden, and all-cause hospitalizations.

MATERIALS AND METHODS

Study Design and Patient Population

Adult (aged ≥18 years), in-center hemodialysis patients who were initially prescribed SO as part of routine care at Fresenius Kidney Care facilities between April 1, 2014, and April 1, 2015, and received 2 years of phosphate-binder prescriptions were included in this analysis. Patients were classified as maintenance SO if they had completed 2 years of uninterrupted SO monotherapy and as discontinued SO if they had discontinued SO therapy within 90 days of SO initiation and switched to other phosphate binder(s) for 2 years (Fig 1). All patients were required to have serum phosphorus measurements and phosphate-binder therapy recorded at baseline (3 months before SO initiation; −Q1 [quarter -1]) and the final quarter (Q8) of the 2-year follow-up period (Q1 through Q8). Phosphate-binder doses were titrated at the discretion of the treating health care providers.

Data Collection, Assessments, and Outcomes

Deidentified clinical and prescription data were extracted retrospectively from the Fresenius Kidney Care clinical data warehouse and Fresenius pharmacy database. Clinical and laboratory parameters evaluated included mean prescribed phosphate-binder pills per day, markers of mineral-bone metabolism (serum phosphorus, plasma intact parathyroid hormone, and serum calcium), nutritional and clearance parameters (serum albumin, normalized protein catabolic rate, and single-pool Kt/V), hemoglobin and iron indexes (ferritin and transferrin saturation), active vitamin D and cinacalcet therapies, and antianemia therapies (intravenous [IV] iron sucrose and IV erythropoiesis-stimulating agents).

Laboratory tests were measured monthly as part of routine clinical practice, except for ferritin and intact parathyroid hormone, which were measured quarterly. All available laboratory measures were averaged over each treatment quarter. For the discontinued SO patient follow-up, clinical and laboratory parameters were included after SO therapy was discontinued. Blood samples were drawn, generally on the same day of each week, using standardized methods at Fresenius Kidney Care facilities and analyzed at Spectra Laboratories (Rockleigh, NJ). In-range serum phosphorus level was defined as ≤5.5 mg/dL as per the NKF-KDOQI upper limit.[9]

Statistical Analysis

Group-wise and between-group comparisons of longitudinal changes in clinical and laboratory parameters were carried out using mixed-effects linear regression and χ^2 tests, and results were summarized as least-squared means and standard errors or number and percent. Unadjusted and covariate-adjusted analyses were conducted to determine mean differences in serum phosphorus levels between the maintenance SO and discontinued SO groups. Corrections for multiple comparisons were not conducted. Between-group comparisons of unadjusted and covariate-adjusted hospital admissions were assessed using generalized estimating equation models under exchangeable correlation structures with zero-inflated Poisson distribution for hospitalization counts and zero-inflated negative binomial distribution for length of hospital admission. Demographic and clinical variables at baseline were assessed as independent predictors and potential confounders of incidence of hospitalizations. A subgroup analysis of patients who were hospitalized for more than 24 hours was also carried out. SAS procedures for nonlinear mixed models (PROC NLMIXED and macro %NLEstimate) were used to obtain incidence rate differences and 95% confidence intervals.

A sensitivity analysis was conducted that included all patients who, although they did not fulfill requirements of SO therapy for 2 years, had SO therapy for at least 90 days (n = 3,047). All months of observation in which phosphate-binder therapy and serum phosphorus levels were recorded were classified into 1 of 3 exposures: SO, non-SO phosphate binders, or SO plus non-SO phosphate binders. Mean serum phosphorus level was calculated for each group using mixed-effects linear regression with exposure as a time-varying covariate.

All analyses were conducted using SAS, version 9.4 (SAS Institute Inc). $P < 0.05$ was considered statistically significant. This study was deemed exempt by the New England Institutional Review Board, Needham, MA (institutional review board # WO 1-6143-1) and was approved for a waiver of informed consent due to deidentified data and the observational nature of the study.

RESULTS

Study Population

In total, 818 patients, 222 maintenance SO and 596 discontinued SO, were included in the study. Baseline demographic and clinical characteristics were largely similar between maintenance SO and discontinued SO groups (Table 1). Mean Charlson Comorbidity Index scores (Table 1) and its individual comorbid conditions (Table S1) were also similar between groups. Patients' phosphate-binder therapies before SO (−Q1) are shown in Table 1, whereas phosphate binders prescribed to discontinued SO patients following SO cessation are summarized in Figure 1. Mean time on SO treatment for discontinued SO patients was 53 days. Almost half (n = 287; 48.1%) the discontinued SO patients were treated with monotherapy non-SO phosphate binder for 2 years and 92 (15.5%) were prescribed non-SO phosphate binder polytherapy for 2 years. The remaining 217 (36.4%) discontinued SO patients switched from SO to different phosphate-binder monotherapies during the 2 years of follow-up. A total of 255 (42.8%) discontinued SO patients switched back to their baseline phosphate binder after discontinuing SO.

Changes in Serum Phosphorus During Treatment

At baseline, mean serum phosphorus level was 6.75 mg/dL (maintenance SO, 6.61 mg/dL; discontinued SO, 6.80 mg/dL), and 142 (17.4%) of the overall patient population (46 [20.7%] maintenance SO, 96 [16.1%] discontinued SO) had serum phosphorus levels ≤ 5.5 mg/

Table 1. Comparison of Baseline Demographic Characteristics Between the Maintenance SO and Discontinued SO Groups

Measure	mSO	dSO	*P*
No. of patients	222	596	NA
Age, y	53.8 ± 14.0	53.8 ± 13.5	0.9
Dialysis vintage, mo	52 ± 52	58 ± 49	0.1
Female sex	96 (43.2%)	279 (46.8%)	0.4
Body mass index, kg/m^2	33.3 ± 18.1	33.5 ± 19.6	0.9
Hemodialysis treatment time/wk, h	10.6 ± 1.8	10.5 ± 1.7	0.6
Race			
White	126 (56.8%)	327 (54.9%)	0.5
African American	87 (39.2%)	232 (38.9%)	
Other	9 (4.1%)	37 (6.2%)	
Hispanic/Latino	41 (18.5%)	101 (17%)	0.8
Diabetes mellitus	120 (54.1%)	316 (53%)	0.8
Congestive heart failure	32 (14.4%)	111 (18.6%)	0.2
Charlson Comorbidity Index score	4.7 ± 2.1	4.8 ± 2.3	0.7
Hospitalizations, incidence rate per 100 patient-y	107.7	119.2	0.09
Baseline phosphate binder			
Sevelamer	111 (50.0%)	249 (41.8%)	0.04
Calcium acetate	47 (21.2%)	142 (23.8%)	
Lanthanum carbonate	15 (6.8%)	29 (4.9%)	
Switch between phosphate binders	19 (8.6%)	94 (15.8%)	
Phosphate-binder polytherapy	30 (13.5%)	82 (13.8%)	
Serum phosphorus, mg/dL	6.6 ± 1.5	6.8 ± 1.3	0.2
Serum calcium, mg/dL	9.3 ± 0.7	9.2 ± 0.7	0.3
Intact parathyroid hormone, pg/mL	533 ± 445	558 ± 442	0.7
Serum albumin, g/dL	4.0 ± 0.2	4.0 ± 0.3	0.3
Single-pool Kt/V	1.7 ± 0.1	1.7 ± 0.1	0.1

Note: Summary estimates are presented as mean ± standard deviation or number (percent) of patients. Conversion values for units: phosphorus in mg/dL to mmol/L, ×0.3229; calcium in mg/dL to mmol/L, ×0.2495.

Abbreviations: dSO, patients who discontinued sucroferric oxyhydroxide therapy and were treated with non-sucroferric oxyhydroxide; mSO, patients who received 2 years of maintenance therapy with sucroferric oxyhydroxide; NA, not applicable; SO, sucroferric oxyhydroxide.

dL. The proportion of patients achieving serum phosphorus levels ≤ 5.5 mg/dL during Q1 to Q8 increased significantly in the maintenance SO group (46 [20.7%] at baseline vs 82 [36.9%] at Q1 to 100 [45%] at Q8; $P < 0.001$) and the discontinued SO group (96 [16.1%] at baseline vs 173 [29%] at Q1 to 190 [31.9%] at Q8; $P < 0.001$; Table 2).

The increase in proportion of patients achieving in-range serum phosphorus levels at Q8 from baseline was higher among maintenance SO patients than discontinued SO patients (+24.3% vs +15.8%; $P < 0.001$; Fig 2). Discontinued SO patients who switched back to their baseline phosphate binder after SO therapy cessation had higher achievement of serum phosphorus levels ≤ 5.5 mg/dL during follow-up compared with those who switched to other phosphate binders (+20.4% vs +15.8%; $P = 0.002$).

For the overall population, the unadjusted mean change in serum phosphorus levels from baseline decreased to a greater extent in the maintenance SO group (−0.66 mg/dL) than in the discontinued SO group (−0.45 mg/dL; $P = 0.014$). After adjusting for baseline confounders (age, serum phosphorus level, and Kt/V), the maintenance SO group continued to have a greater decrease in serum phosphorus levels (−0.63 mg/d) compared with the discontinued SO group (−0.47 mg/dL; $P = 0.02$). Mixed-effects regression analysis showed a significant difference between the 2 groups in unadjusted mean serum phosphorus levels at Q8 (5.98 mg/dL in maintenance SO vs 6.34 mg/dL in discontinued SO; $P < 0.001$) and mean serum phosphorus levels at Q8 adjusted for age, serum phosphorus level, and Kt/V (6.04 mg/dL in maintenance SO vs 6.33 mg/dL in discontinued SO; $P < 0.001$).

We conducted a subgroup analysis excluding patients with severely uncontrolled hyperphosphatemia (serum phosphorus > 8.5 mg/dL) because these patients may not adhere to prescribed therapy (Table S1). This subgroup of 202 maintenance SO and 531 discontinued SO patients had a mean serum phosphorus level of 6.44 mg/dL at baseline (maintenance SO, 6.41 mg/dL; discontinued SO, 6.49 mg/dL), with 143 (19.5%) of the overall population achieving serum phosphorus levels ≤ 5.5 mg/dL (47 [23.3%] maintenance SO and 96 [18.1%] discontinued SO). Achievement of serum phosphorus levels ≤ 5.5 mg/dL during Q1 to Q8 increased more in the maintenance SO group than in the discontinued SO group (+24.9% vs +15.4%; $P < 0.001$). The decrease in unadjusted mean serum phosphorus level from baseline was greater in the maintenance SO group (−0.56 mg/dL) than in the discontinued SO group (−0.31 mg/dL; $P = 0.003$). After adjusting for baseline confounders, the maintenance SO group had a 0.6 mg/dL mean decrease in serum phosphorus levels and the discontinued SO group had a 0.26 mg/dL decrease in serum phosphorus levels ($P < 0.001$).

Table 2. Comparison of Changes in Markers of Mineral Bone Disease and Phosphate-Binder Pill Burden Between the Maintenance SO and Discontinued SO Groups

Measure	Group	−Q1[a] (referent)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Change From −Q1	P[b]
Serum phosphorus, mg/dL	mSO	6.61 (0.1)	6.20 (0.09)[c]	6.14 (0.09)[c]	5.96 (0.1)[c]	5.92 (0.1)[c]	5.93 (0.1)[c]	5.87 (0.1)[c]	5.83 (0.1)[c]	5.98 (0.1)[c]	−0.66	0.014
	dSO	6.80 (0.05)	6.46 (0.06)[c]	6.36 (0.05)[c]	6.34 (0.05)[c]	6.28 (0.05)[c]	6.28 (0.05)[c]	6.30 (0.05)[c]	6.35 (0.05)[c]	6.34 (0.05)[c]	−0.45	
Serum phosphorus ≤ 5.5 mg/dL	mSO	46 (20.7%)	82 (36.9%)[c]	83 (37.4%)[c]	102 (45.9%)[c]	103 (46.4%)[c]	94 (42.3%)[c]	104 (46.8%)[c]	102 (45.9%)[c]	100 (45%)[c]	+24.3%	<0.001
	dSO	96 (16.1%)	173 (29%)[c]	168 (28.2%)[c]	181 (30.4%)[c]	191 (32%)[c]	201 (33.7%)[c]	179 (30%)[c]	170 (28.6%)[c]	190 (31.9%)[c]	+15.8%	
Serum calcium, mg/dL	mSO	9.32 (0.04)	9.27 (0.04)	9.18 (0.04)[c]	9.15 (0.04)[c]	9.11 (0.04)[c]	9.09 (0.04)[c]	9.07 (0.04)[c]	9.03 (0.04)[c]	9.04 (0.04)[c]	−0.18	0.7
	dSO	9.24 (0.02)	9.19 (0.03)[d]	9.15 (0.02)[c]	9.12 (0.02)[c]	9.04 (0.02)[c]	9.09 (0.02)[c]	9.05 (0.02)[c]	9.01 (0.02)[c]	9.01 (0.02)[c]	−0.17	
Intact parathyroid hormone, pg/mL	mSO	533 (32)	544 (32)	567 (32)	605 (32)[d]	610 (31)[d]	621 (32)[c]	590 (32)[d]	609 (32)[d]	608 (32)[d]	+65	0.8
	dSO	558 (20)	601 (23)[d]	581 (20)	590 (20)[d]	594 (20)[d]	607 (20)[d]	649 (20)[c]	661 (20)[c]	676 (20)[c]	+74	
Phosphate binder pills/d	mSO	8.5 (0.1)	4.2 (0.1)[c]	4.4 (0.1)[c]	4.5 (0.2)[c]	4.6 (0.2)[c]	4.9 (0.2)[c]	5.0 (0.1)[c]	5.0 (0.1)[c]	5.1 (0.1)[c]	−3.7	0.2
	dSO	11.6 (0.4)	10.7 (0.5)	10.3 (0.4)[d]	10.4 (0.4)[d]	10.6 (0.4)[d]	10.7 (0.4)[d]	10.8 (0.4)	10.8 (0.4)	10.9 (0.4)	−0.7	

Note: Summary estimates are unadjusted and presented as least-squared means (standard error) or number (percent).

Abbreviations: dSO, patients who discontinued sucroferric oxyhydroxide therapy and were treated with non-sucroferric oxyhydroxide phosphate binder; mSO, patients who received 2 years of maintenance therapy with sucroferric oxyhydroxide; SO, sucroferric oxyhydroxide; Q, quarter.

[a]Group-wise comparisons with −Q1 as reference;

[b]Between-group comparisons of mean change (Q1 to Q8) from baseline (−Q1) for continuous variables and number (percent) at Q8 for categorical variables.

[c]$P < 0.001$,

[d]$P < 0.05$.

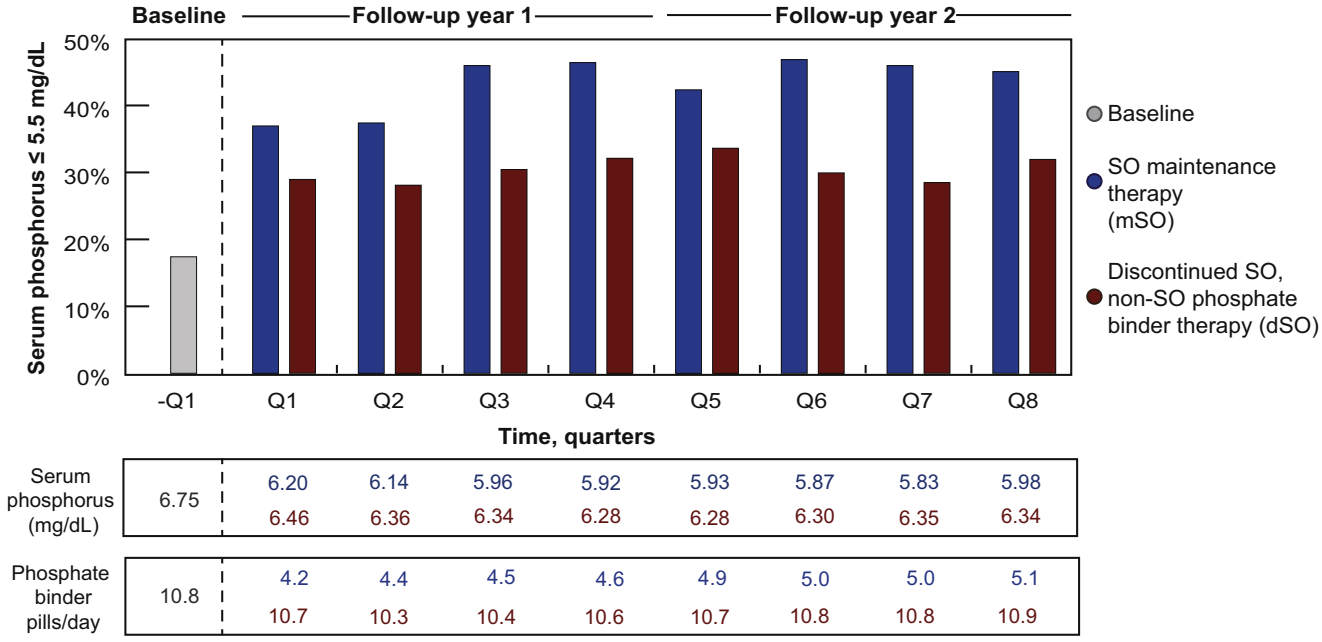

Figure 2. Serum phosphorus control and phosphate-binder pill burden among patients who received 2 years of maintenance therapy with sucroferric oxyhydroxide (mSO) and patients who discontinued sucroferric oxyhydroxide (SO) and were treated with non-SO phosphate binder at baseline and during the 2-year follow-up period (dSO). Baseline percent of patients in range: 20.7% (mSO), 16.1% (dSO). Baseline serum phosphorus levels: 6.61 mg/dL (mSO), 6.8 mg/dL (dSO). Baseline phosphate binder pills per day: 8.5 (mSO), 11.6 (dSO).

A sensitivity analysis was conducted to explore the extent to which requiring complete 2-year follow-up may have influenced results. Included were all 3,047 eligible patients who were treated with SO for less than 2 years. Baseline demographics and clinical characteristics are presented in Table S2. All months of observation were classified into 1 of 3 exposures: SO (34,921 months), non-SO phosphate binders (30,124 months), or SO plus non-SO phosphate binders (30,126 months). A statistically significant decrease in mean serum phosphorus level was observed during SO months (6.55 mg/dL; $P < 0.001$) and SO plus non-SO phosphate-binder months (6.44 mg/dL; $P < 0.001$) when compared with non-SO months (6.66 mg/dL; Table 3).

Phosphate-Binder Pill Burden

Longitudinal changes in daily phosphate-binder pill burden are summarized in Table 2 and Figure 2. Phosphate-binder pill burden decreased from baseline for maintenance SO patients by a mean of 3.7 fewer pills per day (from 8.5 at baseline to 4.2-5.1 pills per day at follow-up), whereas there was no significant change (0.7 fewer pills per day) for discontinued SO patients (from 11.6 to 10.7-10.9 pills per day at follow-up; maintenance SO vs discontinued SO, $P = 0.2$). During the follow-up period, mean daily phosphate-binder pill burden was lower for maintenance SO patients versus discontinued SO patients (5.1 SO pills per day vs 10.9 non-SO phosphate-binder pills per day at Q8; $P = 0.002$). Among patients achieving serum phosphorus levels ≤ 5.5 mg/dL during Q8 of the 2-year follow-up, mean phosphate-binder pill burden decreased among maintenance SO patients (from 7.5 pills per day at baseline to 4.4 pills per day at Q8; $P < 0.001$), but not among discontinued SO patients (9.1 pills per day at baseline to 9.3 pills per day at Q8; $P = 0.3$).

In the subgroup analysis (Table S3) excluding patients with severely uncontrolled hyperphosphatemia (serum phosphorus > 8.5 mg/dL), maintenance SO patients were prescribed 3.6 fewer mean phosphate-binder pills per day (8.4 pills per day at baseline vs 4.2-5.0 pills per day at follow-up), while no change in phosphate-binder pill burden was observed for discontinued SO patients (from

Table 3. Sensitivity Analysis of 3,047 Patients Who Received Less Than 2 Years of SO Therapy

	Non-SO Phosphate Binder mo (referent)	SO Treatment mo	SO + Non-SO Phosphate Binder mo	*P*[a]
Total treatment time, mo	30,124	34,921	30,126	NA
Serum phosphorus, mg/dL	6.66 (0.1)	6.55 (0.1) [a]	6.44 (0.1) [a]	<0.001

Note: Serum phosphorus is presented as least-squared means (standard error)
Abbreviations: NA, not applicable; SO, sucroferric oxyhydroxide.
[a]Group-wise comparisons with −Q1 as reference; $P < 0.001$.

11.5 pills per day at baseline to 10.6-11.0 pills per day at follow-up; maintenance SO vs discontinued SO, P = 0.3).

Changes in Other Mineral Bone Disease Parameters and Concomitant Medication Use

Although there were significant reductions in mean serum calcium levels for both the maintenance SO and discontinued SO groups during the 2-year follow-up, there was no significant difference in mean change in serum calcium levels from baseline between maintenance SO and discontinued SO patients (P = 0.7; Table 2). Similarly, no significant differences in mean change in intact parathyroid hormone levels from baseline were observed between maintenance SO and discontinued SO patients during the follow-up period, although both groups experienced a small increase (Table 2). The proportions of patients who received cinacalcet and vitamin D therapy were similar between both groups (Table S4). Cinacalcet use increased among maintenance SO and discontinued SO patients during the analysis period (+15.3% vs +8.1%; P = 0.8). Vitamin D administration also changed over time, from predominant use of IV vitamin D at the start of the follow-up period to use of both IV and oral vitamin D by the end of the study.

Changes in Nutritional and Clearance Parameters

There was a slight decrease from baseline in mean predialysis weight among discontinued SO patients (−0.56 kg) and increase among maintenance SO patients (+0.03 kg; P = 0.12). There were minimal changes from baseline in single-pool normalized protein catabolic rate and single-pool Kt/V in both the maintenance SO and discontinued SO groups (Table S5). Small reductions in serum albumin levels were observed for both maintenance SO and discontinued SO patients (−0.03 g/dL, for maintenance SO and discontinued SO), with no difference between groups (P = 0.8)

Changes in Hemoglobin and Iron Indexes

The proportion of patients treated with IV iron therapy (iron sucrose) progressively decreased from baseline in both the maintenance SO and discontinued SO groups, with larger decreases in the maintenance SO group (−14% vs −8.2%; P = 0.015; Table S4). Mean IV iron sucrose dose did not change significantly in the maintenance SO group (74.0 mg/mo at baseline vs 74.3 mg/mo at Q8), whereas small increases were observed for discontinued SO patients (75.0 mg/mo at baseline vs 77.2 mg/mo; maintenance SO vs discontinued SO, P = 0.8). There was a greater reduction in the proportion of patients receiving IV erythropoiesis-stimulating agents from baseline in the maintenance SO group (−5%) than in the discontinued SO group (−3.7%; P = 0.5; Table S4).

Significant increases from baseline in mean serum ferritin levels were observed in both maintenance SO (+110 ng/mL) and discontinued SO patients (+105 ng/mL; maintenance SO vs discontinued SO, P = 0.9; Table 4). Small increases in transferrin saturation from baseline were observed in the maintenance SO group (+1.8%), whereas levels slightly decreased in the discontinued SO group (−0.4%; P = 0.002). Small increases in hemoglobin levels were observed in both groups (P = 0.5).

Hospitalizations and Length of Hospital Admissions

At baseline, incidence rates of hospitalizations per 100 patient-years were similar in the maintenance SO (107.7) and discontinued SO groups (119.2; P = 0.09). During the 2-year follow-up, we observed a lower incidence rate of hospitalizations per 100 patient-years among maintenance SO patients (128.6) compared with discontinued SO patients (156; unadjusted incidence rate ratio, 0.82; 95% confidence interval, 0.68-1.00; P = 0.05). After adjustment for baseline hospitalizations, Charlson Comorbidity Index score, and year of start of follow-up, maintenance SO patients had 35.6 fewer hospital admissions per 100 patient-years compared with discontinued SO patients (P = 0.02; Table 5). A separate analysis of hospital admissions lasting longer than 24 hours and length of hospital admissions is presented in Table 5.

DISCUSSION

This 2-year comparative database analysis used a novel study design in which patients who had discontinued SO therapy for other phosphate binder(s) were selected to serve as an active control group for patients who maintained SO therapy. These 2 groups had similar selection factors because both were prescribed SO as part of routine care. This enabled us to compare the effectiveness of SO therapy with other routinely prescribed phosphate-binder therapies in groups with balanced baseline characteristics, including demographics, laboratory measurements, and comorbid conditions.

Overall, 676 (82.6%) patients included in our analysis had serum phosphorus levels > 5.5 mg/dL at baseline despite receiving phosphate-binder therapy. This proportion is substantially higher than the average rate of hyperphosphatemia (~36%) reported for the US dialysis patient population,[8] suggesting that SO was mainly prescribed to difficult-to-treat patients, which may limit the generalizability of the results. The proportion of patients in the maintenance SO group achieving in-target serum phosphorus levels (≤5.5 mg/dL) increased by up to 120% during the 2-year follow-up period, which was higher than in the discontinued SO group. Reductions from baseline in mean serum phosphorus levels were greater in the maintenance SO group compared with the discontinued SO group during the 2-year follow-up.

The observed improvements in serum phosphorus control among maintenance SO patients were achieved with ~50% fewer phosphate-binder pills versus the discontinued SO group (5.1 SO pills per day vs 10.9 non-SO phosphate-binder pills per day at Q8; P = 0.002). For

Table 4. Comparison of Changes in Ferritin, Transferrin Saturation, and Hemoglobin Between Maintenance SO and Discontinued SO Patients

Measure	Group	−Q1[a] (referent)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Change From -Q1	*P*[b]
Ferritin, ng/mL	mSO	973 (32)	1,007 (32)	1,088 (31)[c]	1,118 (31)[c]	1,118 (31)[c]	1,113 (31)[c]	1,110 (31)[c]	1,114 (31)[c]	1,100 (31)[c]	+110	0.9
	dSO	965 (21)	1,046 (26)[d]	1,044 (21)[c]	1,044 (21)[c]	1,081 (21)[c]	1,069 (21)[c]	1,098 (21)[c]	1,073 (20)[c]	1,084 (21)[c]	+105	
Transferrin saturation, %	mSO	34.9 (0.7)	36.8 (0.7)[d]	36.9 (0.7)[d]	37.3 (0.7)[c]	37 (0.7)[d]	37 (0.7)[d]	37.1 (0.7)[d]	36.0 (0.7)	35.4 (0.7)	+1.8	0.002
	dSO	34.3 (0.4)	34.3 (0.5)	34.3 (0.4)	33.7 (0.4)	33.9(0.4)	33 (0.4)[d]	33.9 (0.4)	33.6 (0.4)	33.7 (0.4)	−0.4	
Hemoglobin, g/dL	mSO	11.0 (0.1)	11.0 (0.1)	11.1 (0.1)[c]	11.0 (0.1)	11.1 (0.1)[d]	11.0 (0.1)	11.0 (0.1)	11.0 (0.1)	11.1 (0.1)[c]	+0.08	0.5
	dSO	10.9 (0.04)	10.8 (0.04)[d]	10.9 (0.04)	10.9 (0.04)	10.8 (0.04)[c]	10.9 (0.04)	10.9 (0.04)	11.0 (0.04)[c]	11.0 (0.04)[c]	+0.04	

Note: Summary estimates are unadjusted and presented as least-squared means (standard error).
Abbreviations: dSO, patients who discontinued sucroferric oxyhydroxide therapy and were treated with non-sucroferric oxyhydroxide phosphate binder; mSO, patients who received 2 years of maintenance therapy with sucroferric oxyhydroxide; Q, quarter; SO, sucroferric oxyhydroxide.
[a]Group-wise comparisons with −Q1 as reference.
[b]Between-group comparisons of mean change (Q1 to Q8) from baseline (−Q1) for continuous variables and number (percent) at Q8 for categorical variables.
[c]$P < 0.001$.
[d]$P < 0.05$.

maintenance SO patients, mean daily phosphate-binder pill burden decreased by ∼40% from baseline after switching to SO (from 8.5 pills per day at baseline vs 5.1 SO pills per day at Q8; $P < 0.001$), whereas phosphate-binder pill burden was unchanged for discontinued SO patients (11.6 pills per day at baseline vs 10.9 pills per day at Q8; $P = 0.2$). Among patients achieving serum phosphorus levels ≤ 5.5 mg/dL during Q8, pill burden at Q8 decreased from baseline among maintenance SO patients (−3.1 pills per day), but not among discontinued SO patients (+0.2 pills per day; $P = 0.12$). Previous studies have demonstrated that high phosphate-binder pill burden is associated with reduced adherence to phosphate-binder therapy among dialysis patients, which has in turn been linked to increased serum phosphorus levels.[10,11,13] The 40% reduction in pill burden achieved with SO in this study is a potential advantage with respect to improving patient adherence. Improved patient adherence may have been a contributing factor toward the improved serum phosphorus control observed among patients prescribed 2 years of SO therapy.

A lower rate of hospital admissions among maintenance SO patients versus discontinued SO patients was observed. To model the potential cost savings associated with fewer hospital admissions with SO treatment, we applied methodology used in a previous analysis by Rodby et al[18] in 2014 for another iron-based phosphate binder, ferric citrate. Hospitalization expenditure data from the 2018 US Renal Data System Annual Data Report (specifically, total inpatient expenditure per hemodialysis patient: $27,654),[19] along with a hospitalization rate per year of 1.73846, were used to calculate an average cost per hospitalization of $15,907.18. The potential cost saving was calculated by multiplying the average cost of hospitalization with the adjusted incidence rate difference per 100 patient-years (35.6 fewer hospitalizations). The economic model estimated a potential annual cost saving of $566,295 per 100 patients for those completing 2 years of SO therapy.

The findings of this current analysis are similar to those from previous real-world studies of SO.[16,17] A recent analysis evaluating the effectiveness of SO in hemodialysis patients who switched to SO monotherapy for a 1-year period[17] demonstrated a 2-fold increase from baseline in the proportion of patients achieving in-range serum phosphorus levels (18% to 36%) and a 50% reduction in phosphate-binder pill burden (8.5 to 4.0–4.3 pills per day). In comparison, in our 2-year analysis, a greater increase in the proportion of patients who achieved in-range serum phosphorus levels was observed (21% at baseline to 47% at Q8), although patients received on average a higher number of SO pills (5.1 SO pills per day at Q8). These findings suggest that some patients may require a higher number of SO pills to achieve in-target serum phosphorus concentrations.

Our findings on serum phosphorus control and phosphate-binder pill burden were also consistent with observations from the SO phase 3 study[14] and its 28-week

Table 5. Crude and Adjusted Rates of Hospital Admission Among Maintenance SO and Discontinued SO Patients During the 2-year Follow-up

	Incidence Rate (95% CI), per 100 PY	Incidence Rate Ratio (SE)	Incidence Rate Difference (95% CI), per 100 PY	*P*	Length of Hospital Admission (95% CI), d per 100 PY	*P*
All hospital admissions, unadjusted						
mSO	128.6 (109.2 to 151.5)	0.824 (1.104)	−27.4 (−40.2 to −14.7)	0.05	347 (287 to 419)	0.07
dSO (referent)	156.0 (138.8 to 175.5)				424 (378 to 475)	
All hospital admissions, multivariate models[a]						
mSO	108.3 (83.8 to 139.6)	0.752 (1.138)	−35.6 (−48.5 to −17.8)	0.02	294 (212 to 410)	0.1
dSO (referent)	143.9 (125.6 to 164.8)				419 (325 to 457)	
Hospital admissions > 24 h, unadjusted						
mSO	113.3 (96.2 to 133.4)	0.81 (1.106)	−26.6 (−38.5 to −14.6)	0.04	336 (327 to 458)	0.04
dSO (referent)	139.9 (124.8 to 156.7)				419 (373 to 472)	
Hospital admissions > 24 h, multivariate models[a]						
mSO	91.8 (70.8 to 119.0)	0.70 (1.145)	−39.6 (−52.8 to −22.5)	0.006	297 (222 to 397)	0.04
dSO (referent)	131.4 (114.3 to 151.1)				422 (360 to 495)	

Abbreviations: CI, confidence interval; dSO, patients who discontinued sucroferric oxyhydroxide therapy and were treated with non-sucroferric oxyhydroxide phosphate binder; IV, intravenous; mSO, patients who received 2 years of maintenance therapy with sucroferric oxyhydroxide; PY, patient-year; SO, sucroferric oxyhydroxide.

[a]The following baseline variables were assessed as independent predictors and potential confounders: age, dialysis vintage, sex, body mass index, race, dialysis treatment time per week, primary cause of end-stage kidney disease, hospital admissions at baseline, Charlson Comorbidity Index score, year of start of follow-up, baseline phosphate binder, markers of mineral bone disease (serum phosphorus, serum calcium, and intact parathyroid hormone), nutritional and clearance parameters (serum albumin, single-pool normalized protein catabolic rate, and single-pool Kt/V), hemoglobin and iron indexes (serum ferritin and transferrin saturation), and use of IV iron, IV erythropoiesis-stimulating agents, IV vitamin D, oral vitamin D, and cinacalcet. Potential confounders for incidence of hospitalizations included Charlson Comorbidity Index score, hospital admissions at baseline, and year of start of follow-up. Potential confounders for length of hospital admissions included hospital admissions at baseline and baseline serum ferritin level.

extension,[15] in which the SO therapy provided similar serum phosphorus level reductions during a 52-week treatment period and was associated with a lower mean daily pill burden than the comparator, sevelamer carbonate (3.3 SO pills per day vs 8.7 sevelamer pills per day for the 1-year study period).[15] The changes we observed in iron parameters are also consistent with those in the phase 3 study, which indicated that such changes were primarily driven by concomitant IV iron use and that iron absorption from SO was minimal.[20]

Our study had several limitations. It was a retrospective observational analysis that used existing electronic clinical records. Data relating to treatment indication, adherence, or tolerance were not available. The reasons for SO therapy discontinuation by discontinued SO patients were not captured, but may include lack of effectiveness, nontolerability, nonadherence, insurance coverage, and out-of-pocket costs. Sensitivity analysis was conducted to address the potential for bias from SO discontinuation during follow-up. Although patients received dietary advice from dietitians using approved educational materials, no direct information about nutritional habits and dietary phosphorus intake was recorded. Prescription data may provide accurate insight into prescribed pill burden but cannot be used as a surrogate for patient adherence with prescribed regimens.

Corrections for multiple comparisons were not conducted. Although we adjusted for available potential confounders, we could not conduct a propensity score analysis and could not determine the impact of unmeasured confounders such as socioeconomic status on the differences observed in changes in serum phosphorus levels, hospitalization rates, and length of hospitalizations. During the 2 years of follow-up, intact parathyroid hormone control varied and use of other medications (such as active vitamin D and cinacalcet) that may affect phosphorus control changed similarly in both the maintenance SO and discontinued SO groups. These practice pattern changes could have affected our results.

In summary, this retrospective database analysis used a novel study design to compare the long-term real-world effectiveness of SO therapy versus other prescribed phosphate-binder therapies in difficult-to-treat patients with uncontrolled hyperphosphatemia. We found that patients who completed 2 years of SO therapy had lower mean serum phosphorus levels, were more likely to achieve in-range serum phosphorus levels (≤5.5 mg/dL), and were prescribed ∼50% fewer phosphate-binder pills per day compared with patients who discontinued SO therapy and switched to other phosphate binders. Adjusted incidence rate difference per 100 patients found 35.6 fewer annual hospitalizations among patients who completed 2 years of SO therapy. The economic model based on the decrease in hospitalizations estimated a potential annual cost saving of $566,295 per 100 patients for patients completing 2 years of SO therapy.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Comparison of Baseline Comorbid Conditions Between Maintenance SO and Discontinued SO Patients

Table S2: Demographic Characteristics of 3,047 Patients in the Sensitivity Analysis Cohort Who Received < 2 Years of SO Therapy

Table S3: Comparison of Changes in Serum Phosphorus and Phosphate Binder Pill Burden Among 202 Maintenance SO and 531 Discontinued SO Patients With Baseline Serum Phosphorus ≤8.5 mg/dL

Table S4: Comparison of Changes in the Prescription Patterns of Oral Cinacaclet, Oral and IV Vitamin D, IV Iron, and IV Erythropoietin Agents Among Maintenance SO and Discontinued SO Patients

Table S5: Changes in Nutritional and Clearance Parameters Among Maintenance SO and Discontinued SO Patients

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