Impact of Prescription Benefit Coverage Limits on Sevelamer Hydrochloride Adherence for Patients with ESRD

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Objective: To assess the impact of prescription benefit coverage on medication adherence in Medicare-eligible members diagnosed with end-stage renal disease taking sevelamer hydrochloride.

Methods: This pilot study involved a retrospective analysis of patients with end-stage renal disease taking sevelamer, with an annual cap on brand prescription drug spending compared with those without a cap. We compared sevelamer adherence and discontinuation proportions between the 2 groups of Medicare patients in 2003 and 2004. Medication adherence was calculated based on the proportion of available days covered in relationship to capped versus noncapped pharmacy benefit.

Results: Rate ratios showed that in 2003, the patients taking sevelamer under a capped benefit (N = 43) had 27% fewer days of drug use compared with those (N = 88) without a capped benefit (relative risk, 0.73; 95% CI, 0.58-0.93). Similarly, in 2004, those taking sevelamer under the capped benefit (N = 21) had 33% fewer days of drug use compared with those (N = 117) without a capped benefit (relative risk, 0.67; 95% CI, 0.46-0.96).

Conclusions: Medication adherence was significantly lower for patients with a capped brand-name drug benefit. These findings provide insight into potential drug utilization patterns, including for sevelamer, under the Medicare Part D benefit, where members could face significant out-of-pocket expenditures once coverage limits are reached. [*AHDB*. 2009;2(6):242-250.]

Hyperphosphatemia is prevalent among patients with end-stage renal disease (ESRD) and continues to be an important and challenging area for drug therapy. The kidneys play a key role in maintaining normal serum phosphorus levels, which is impaired at an estimated glomerular filtration rate (GFR) of 50 mL/min to 60 mL/min.[1,2] An adaptive process by the kidneys, which involves an increase in circulating parathyroid hormone (PTH) with normal calcitriol levels, helps to control phosphorus at this low GFR value.[1,2] Once the GFR decreases to 25 mL/min to 30 mL/min, the PTH elevation and low levels of calcitriol cannot maintain a normal phosphorus level, leading to hyperphosphatemia.[1,2] Hyperphosphatemia, in addition to elevated calcium phosphorus product and elevated PTH, is associated with significant morbidity and mortality.[1]

Failure to adequately control elevated serum phosphorus levels can result in cardiovascular events, including coronary artery disease (CAD), uncontrolled hyperparathyroidism, and fractures.[1] These complications carry a significant economic burden and untoward personal costs associated with hospitalization, increased higher healthcare resource utilization, decreased quality of life, and premature death.[3-7]

The Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines published by the National Kidney Foundation emphasize the importance of serum phosphorus control in patients with ESRD.[8] The K/DOQI guidelines recommend the initiation of oral phosphate binders when serum phosphorus and intact PTH levels cannot be kept within the

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target range with dietary phosphorus restriction alone. Calcium-containing phosphate-binding medications are effective; however, they carry the risk of elevating serum calcium levels above the target range in patients with ESRD.[8,9] Hypercalcemia has been linked to increased mortality risk in patients with ESRD.[5,10-14]

The K/DOQI guidelines suggest a preference for phosphate binders—which are noncalcium, nonmagnesium, and nonaluminum, such as sevelamer hydrochloride (Renagel; henceforth sevelamer)—in patients on dialysis with severe vascular and/or other soft-tissue calcifications. The guidelines also suggest the use of these agents in patients with hypercalcemia to control phosphorus levels.[8,11] A recent study showed that 53% of patients with advanced chronic kidney disease fulfilled at least 1 criterion for the use of sevelamer.[15]

Sevelamer is a polymeric compound that binds phosphate within the intestinal lumen, limiting absorption of and decreasing serum phosphate concentrations without altering calcium, aluminum, or bicarbonate concentrations.[16] It is not currently available as a generic product. For some patients, its use may be limited by its high cost.[17] In addition, reduced adherence to sevelamer in patients with ESRD because of financial barriers can significantly increase utilization of high-cost drivers of healthcare, such as hospitalizations and outpatient visits.

In 2003, the average wholesale price (AWP) for sevelamer was $1.31/tablet or between $2832 and $8484 per year.[18] In 2004, the AWP increased to $1.42/tablet or between $3072 and $9204 annually for an individual[19] (based on a dosing frequency of 2-6 tablets/meal and 3 meals/day). Limitations with prescribing a phosphorus-restricted diet in addition to limitations in phosphorus removal by conventional dialysis, make the use of a noncalcium-based phosphate binder, such as sevelamer, the option to managing hyperphosphatemia without increasing the risk for hypercalcemia.[5] Patients who are unable to comply with sevelamer therapy because of cost constraints are often left with the alternative of calcium-based phosphate binders and may be at risk for subsequent complications secondary to hypercalcemia.

In one study, patients treated with sevelamer had a 50% lower likelihood of hospitalization and had lower overall annual costs by more than $16,500 per patient than patients not receiving this drug.[20] However, nonadherence to drug therapy has been a significant problem in the ESRD population.[21-23] Nonadherence to hemodialysis treatment, as assessed by the number of missed dialysis sessions and hyperphosphatemia, has been associated with increased mortality.[6] In that study, the relative risk for skipping 1 or more dialysis treatments per month was 1.30, and the mortality risk for serum phosphorus >6.5 mg/dL was 1.27 relative to a serum phosphorus of 2.4 mg/dL to 6.5 mg/dL.[6,7] The direct cost-related nonadherence rate in the United States for patients with ESRD is 29%.[24]

KEY POINTS

- Previous studies have shown that drug benefit coverage design can affect patient medication adherence.
- Putting a cap on total drug spending has been associated with decreased medication adherence, resulting in poor clinical outcomes.
- Results of this study showed that sevelamer hydrochloride adherence was significantly lower for Medicare patients with end-stage renal disease with a capped brand-name drug benefit compared with those without a capped benefit.
- Reduced drug utilization may likely have been the result of greater patient cost-sharing. This utilization pattern has ramifications on biochemical outcomes in this patient population and potentially in other patients using brand-name medications.

Drug Benefit and Adherence

Caps on total drug spending have been associated with decreased medication adherence and reduced control of systolic blood pressure, low-density lipoprotein (LDL) cholesterol, and glycosylated hemoglobin in patients with hypertension, hyperlipidemia, and diabetes, respectively.[25] Patients with drug coverage limits have increased emergency department visits and hospitalizations, which may have a direct impact on total healthcare spending.[25-27]

There is limited research examining the impact of sevelamer adherence within a capped drug benefit for patients with ESRD. An appropriate way to measure sevelamer adherence within a Medicare managed care population is by using the proportion of days covered (PDC).[28,29] PDC is the number of days in the measurement period covered by prescription claims for the same medication or another in its therapeutic category as defined by the Pharmacy Quality Alliance.[30] The PDC threshold is the level (typically 80%) above which the medication has a reasonable likelihood of achieving most of its potential clinical benefit.

Patients with ESRD are eligible for prescription drug coverage under Medicare Part D. The standard Part D benefit includes limits on total drug spending. For

Table 1 Copays for Sevelamer in the Capped Group, 2003 and 2004

	2003		2004	
Cap	$30 copay, N (%)	$50 copay, N (%)	$30 copay, N (%)	$50 copay, N (%)
$500	2 (4.7)	14 (32.6)	NA	NA
$1000	NA	NA	NA	9 (42.9)
$1500	0	27 (62.8)	NA	12 (57.1)

example, in 2006 the total drug spending limit was $2250, after which patients enter a coverage gap and are responsible for 100% of the cost of all medications until catastrophic coverage takes effect. The total drug spending limit for Medicare Part D increased to $2400 and $2510, respectively, in 2007 and 2008.[31,32] Sevelamer is a tier 2 (preferred brand-name) drug in most Medicare Part D plans.[33] Patients with ESRD taking sevelamer could be particularly vulnerable to spending limits in the Part D benefit, because they may be responsible for 100% of medication costs once they reach the coverage gap threshold.

The primary objective of this pilot study was to compare adherence and discontinuation proportions in patients with ESRD receiving sevelamer under a capped brand-name prescription benefit in Medicare plans and in retiree patients who have no caps in non-Medicare plans offered by Kaiser Permanente Colorado. Secondary end points included specific biochemical outcomes for patients with ESRD within a capped and a noncapped prescription benefit.

Methods

Kaiser Permanente Colorado is an integrated healthcare delivery system for more than 400,000 members in the Denver-Boulder metropolitan area. The physicians of the Colorado Permanente Medical Group contract exclusively with the Kaiser Foundation Health Plan to provide comprehensive healthcare services. Medicare-eligible members represent approximately 15% of Kaiser Permanente Colorado membership.

In 2003 and 2004, Medicare patients in a Medicare+Choice plan had a $30 or $50 copay for brand-name medications, with a $500 (2003 and 2004), $1000 (2004), or $1500 (2003) capped benefit. Members paid their copays until the prescription drug cap was met each year. At that point, they were responsible for 100% of the cost of all brand-name prescription drugs. The capped benefit differed slightly between 2003 and 2004. In 2004, patients with a Medicare+Choice plan also had a $300 deductible for brand-name medications, after which they faced a cap on brand-name drug spending.

Table 2 Distribution of Copays for Sevelamer in the Noncapped Group, 2003 and 2004

Prescription drug copay, $	2003 N (%)	2004 N (%)
3	3 (3.4)	3 (2.6)
5	5 (5.7)	4 (3.4)
7	1 (1.1)	0
10	16 (18.2)	20 (17.1)
15	6 (6.8)	5 (4.3)
20	24 (27.3)	34 (29.1)
25	2 (2.3)	9 (7.7)
30	19 (21.6)	23 (19.7)
40	1 (1.1)	5 (4.3)
50	11 (12.5)	14 (12.0)

The annual copay distribution for sevelamer in the capped group is shown in **Table 1**. A large proportion of patients in 2003 (95%) and 2004 (100%) had prescription copays of $50 for this medication.

The noncapped prescription benefit did not have any limits on prescription drug spending and represented a retiree Medicare population with employer-sponsored coverage. Retiree-based Medicare patients in the noncapped group typically paid a copay for brand-name medications ranging from $5 to $40. **Table 2** shows the annual distribution of copays for sevelamer in the noncapped group. In 2003 and 2004, a large proportion of patients in the noncapped group had copays of $20 (27% and 20%, respectively) or $30 (15% and 20%, respectively).

All patients with documented ESRD receiving sevelamer during the first 6 months of 2003 and 2004 were identified using pharmacy claims data. Inclusion criteria were continuous dialysis (peritoneal or hemodialysis) between January 1, 2003, and December 31, 2004, and continuous health plan membership with pharmacy benefits for this period. Because of a lack of awareness of the Medicare drug discount card (instituted in 2004), and the difficulty in identifying patients who had the card, the potential impact of the discount was excluded.[34] The sevelamer index date was defined as the first sevelamer dispensed in each calendar year. All dispensing events were captured through the end of each calendar year. Patients were stratified into groups according to type of Medicare drug coverage (capped or noncapped). The 2 groups were kept separate, because the capped benefits changed from 2003 to 2004.

Sevelamer adherence was defined as the PDC during

Table 3 Characteristics of Patients with Sevelamer Dispensing in the First 6 Months of 2003 and 2004

	2003 (N = 131)					2004 (N = 138)				
	Capped (n = 43)		Noncapped (n = 88)			Capped (n = 21)		Noncapped (n = 117)		
Characteristic	Median	(5th, 95th percentile)	Median	(5th, 95th percentile)	*P*	Median	(5th, 95th percentile)	Median	(5th, 95th percentile)	*P*
Age at first dispensing	62 yr	(33, 85 yr)	61 yr	(34, 78 yr)	.644	69 yr	(49, 88 yr)	62 yr	(27, 81 yr)	.014
Distinct oral medications, N[a]	6	(2, 15)	7	(2, 15)	.245	6	(3, 12)	7.5	(2, 16)	.134
Sex	**N**	%	**N**	%		**N**	%	**N**	%	
Female	16	37.2	40	45.4		8	38.1	50	42.7	
Male	27	62.8	48	54.6		13	61.9	67	57.3	
Comorbid conditions										
CAD	29	67.4	28	31.8	.001	11	52.4	47	40.2	.296
Diabetes mellitus	37	86.1	78	88.6	.670	20	95.2	100	85.5	.307
MDD	0	0.0	4	4.6	NA	0	0.0	2	2.3	NA
CHF	8	18.6	22	25.0	.413	7	33.3	24	20.5	.254
Atrial fibrillation	8	18.6	6	6.8	.067	6	28.6	8	6.8	.008
Hypertension	32	74.4	66	75.0	.942	15	71.4	92	78.6	.569
Parathyroidectomy	5	11.6	11	12.2	.921	1	4.8	8	6.7	.735

[a]Distinct medications calculated by medications with a total of at least 90-day supply over the year summed up by the first 8 digits in the generic product identifier code (down to the drug name level).

CAD indicates coronary artery disease; CHF, chronic heart failure; MDD, major depressive disorder.

calendar years 2003 and 2004. The PDC was measured as a continuous variable and was calculated by dividing the total number of days supply of sevelamer dispensed by the total number of days between the index dispensing of sevelamer and the end of both calendar years.[27-30]

Patients were considered to have discontinued the use of sevelamer if they only had 1 prescription of the drug filled in each calendar year. Discontinuation proportions were calculated by dividing the number of patients who discontinued sevelamer by the total number of patients receiving a sevelamer prescription in the capped and noncapped group for each year.

Laboratory test results were obtained through a review process of each patient's charts. The last measured values for the relevant clinical markers were collected each month for each patient, and the average of these values was used as the outcome measure.

Medical and pharmacy data from administrative sources and patient chart reviews were used to identify patient age (based on the index date for a sevelamer dispensing); sex; comorbid conditions (major depressive disorder, atrial fibrillation, chronic heart failure [CHF], hypertension, CAD, diabetes mellitus); procedure for parathyroidectomy; pharmacy benefit structure (capped vs noncapped); concurrent drug use (calcimimetics; calcium-, aluminum-, or magnesium-containing phosphate binders; and vitamin D analog therapy); associated laboratory test results (corrected calcium-phosphorus product; and corrected serum calcium, serum phosphorus, and intact PTH).

For both calendar years, comorbid conditions of interest were identified by the codes of the *International Classification of Diseases, 9th Revision*, and procedures of interest were identified by the *Current Procedural Terminology, 4th Edition*. Although beneficiaries have the ability to change coverage during the year, pharmacy benefit structure at the index sevelamer prescription was assumed to continue during each calendar year. Concurrent drug use was primarily identified using National Drug Codes.

Statistical significance of differences for the descriptive variables noted above was tested using the Wilcoxon rank sum or chi-square tests for continuous and categorical variables, respectively. Associations between pharmacy benefit coverage and medication adherence and discontinuation were evaluated using Poisson regression modeling with the canonical log-link function and an offset parameter to accommodate the effect of unequal length of the individual follow-up period.[35] The model was fit with a correction for

Table 4 Characteristics Associated with Medication Adherence for Sevelamer Users

Variable characteristics	2003 Adjusted rate ratios (95% CI)	2004 Adjusted rate ratios (95% CI)
Noncapped benefit referent	0.73 (0.58-0.93)[a]	0.67 (0.46-0.96)[a]
No parathyroidectomy referent	0.50 (0.33-0.76)[b]	0.65 (0.37-1.17)
Continuous number of medications	0.99 (0.98-1.00)	1.00 (0.99-1.02)
Continuous age at first dispensing	1.00 (0.99-1.01)	1.00 (0.99-1.01)
Male referent	1.14 (0.94-1.39)	1.02 (0.82-1.27)
No depression referent	0.88 (0.50-1.55)	0.59 (0.21-1.67)
No atrial fibrillation referent	0.84 (0.59-1.19)	0.93 (0.62-1.40)
No hypertension referent	1.02 (0.81-1.29)	0.87 (0.66-1.14)
No CHF referent	1.14 (0.90-1.45)	NA
No CAD referent	NA	0.99 (0.79-1.25)
No metoprolol/atenolol use referent	1.05 (0.85-1.29)	1.20 (0.95-1.53)
No calcimimetics use referent	NA	0.98 (0.72-1.34)
Corrected Ca × P product ≤55 mg^2/dL^2 referent	1.16 (0.87-1.55)	1.01 (0.74-1.38)
No concurrent calcium-based phosphate binder referent	0.91 (0.72-1.15)	0.78 (0.58-1.05)

[a]P <.05 (significant difference).
[b]P <.01 (significant difference).
Ca × P indicates calcium-phosphorus product; CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval.

overdispersion. Rate ratios were tabulated to compare the capped and noncapped groups. Logistic regression analysis was used to determine the relationship between pharmacy benefit coverage discontinuation proportions for sevelamer. Analyses were conducted using SAS 9.1 (SAS Institute; Cary, NC).

Results

Table 3 describes the characteristics of patients with ESRD receiving sevelamer during the first 6 months of 2003 and 2004. In 2003, 131 patients met the eligibility criteria: 43 (32.8%) patients were in the capped group and 88 (67.2%) in the noncapped group. In 2004, 138 patients met the eligibility criteria: 21 (15.2%) patients in the capped group and 117 (84.8%) in the noncapped group. The top 3 diagnoses for patients in the capped group in 2003 were diabetes mellitus, atrial fibrillation, and hypertension, and in 2004 diabetes mellitus, hypertension, and CAD. Similar trends were observed in the noncapped group.

In 2003, the capped and noncapped groups were similar in most characteristics, except CAD, where the capped group had a higher percentage of members than the noncapped group (P = .001). In 2004, the noncapped group was younger than the capped group and had a lower percentage of members with atrial fibrillation.

The capped-group patients faced greater cost-sharing for sevelamer after they reached their cap (results not shown). In 2003, the mean copay for patients taking sevelamer in the capped group was $50 before the cap was reached and $395 after the cap was reached. In 2004, the mean copay was $160 before the cap was reached and $264 after. In 2003, the unadjusted median PDC was 40.0% for the capped group and 66.3% for the noncapped group; in 2004 the unadjusted median PDC for the capped group was 40.4% compared with 59.2% for the noncapped group. In 2003 and 2004, 60.5% of the patients in the capped group had PDCs <50% compared with 33% in the noncapped group. The unadjusted proportion of patients who discontinued sevelamer was 28% in 2003 and 19% in 2004 in the capped group and 15% in 2003 and 17% in 2004 in the noncapped group. None of these differences were significant.

Adjusted rate ratios are shown in **Table 4**. Adjusted analysis showed that factors influencing the PDC in 2003 included pharmacy benefit group and presence of the parathyroidectomy procedure. Adjusted rate ratios reveal that in 2003 patients with a capped benefit had 27% fewer days of sevelamer use compared with the noncapped benefit (odds ratio [OR], 0.73; 95% confidence interval [CI], 0.58-0.93). The 2004 adjusted rate ratios showed those with a capped benefit have 33% fewer days of sevelamer use compared with the noncapped benefit (OR, 0.67; 95% CI, 0.46-0.96).

None of the variables, including the type of pharmacy benefit, were associated with discontinuation of sevelamer in 2003 and 2004 (**Table 5**).

In 2003, there was a significant difference in the corrected serum calcium level, serum phosphorus level, and the corrected calcium-phosphorus product in patients with ESRD in the capped group compared with those in the noncapped group (**Table 6**). The intact PTH values did not differ significantly between the capped and noncapped groups.

Patients with ESRD in the noncapped group had slightly lower corrected serum calcium and serum phosphorus values but much lower corrected calcium-phosphorus product values (a difference of 4.7 mg/dL). In 2004, results were similar to 2003, except that the corrected calcium-phosphorus product was not significantly different between the 2 groups.

Discussion

Although the ESRD population accounts for less than 1% of the entire US population, it continues to increase at a rate of 3% annually across all races and age-groups.[36] Total Medicare spending in 2006 was nearly $355 billion; ESRD costs rose to $23 billion (6.4% of the total Medicare budget).[36] Patients with ESRD have many comorbidities, and a majority of the older patients take 5 or more medications.[36] The leading cause of ESRD is diabetes (44.8%), followed by hypertension (26.8%) and glomerulonephritis (12.8%).[36]

Drug therapy for patients with ESRD is complex, requiring many oral and injectable medications, some of which require multiple doses each day. Attempts to use behavioral models to predict medication nonadherence have suggested complex interrelationships between psychologic factors and adherence in this patient population.[21] A recent review suggests health beliefs (eg, perceptions of self-efficacy with regard to taking medication), social support (eg, support of friends, family, and renal staff), family dynamics (eg, family problems caused by the patient's illness), and personality traits (eg, low conscientiousness) as significant predictors of nonadherence to phosphate-binding medications in these patients.[37]

Results of our analysis show that adherence to sevelamer treatment was 27% lower in the capped group in 2003 and 33% lower in 2004 compared with the noncapped group. Patients with ESRD were taking an average of 10 to 12 medications in both years. The total annual out-of-pocket (OOP) expenses for sevelamer were 26% and 57% higher for patients in the capped group compared with patients in the noncapped group in 2003 and 2004, respectively.

These rates of adherence are higher than those reported in a previous study, although that study only examined patient self-reports of cost-related nonadherence, which are typically lower than what is examined in claims data, because of recall bias issues.[24] In addition, our small sample size did not allow us to examine whether the use of sevelamer was influenced by members reaching the capped portion of their prescription benefit. However, despite the generosity of the noncapped benefit, median adherence rates were only 40.4% in 2003 and 59.2% in 2004. Thus, although cost is a factor that may affect adherence, other factors not examined in this pilot study may affect adherence as well.

Our findings also suggest that lower adherence to sevelamer treatment may have been associated with less desirable biochemical outcomes. The K/DOQI guidelines recommend a serum phosphorus level of 3.5 mg/dL to 5.5 mg/dL for patients with ESRD, a corrected serum calcium level of 8.4 mg/dL to 9.5 mg/dL, and a goal for corrected calcium-phosphorus product of 55 mg^2/dL^2.[8] The corrected serum calcium values were above K/DOQI targets in the capped group in both years. The serum phosphorus values and corrected calcium–phosphorus product were at the high end of the target goal range in the capped group in 2003.

Although this pilot study was not designed to evaluate the clinical significance of the biochemical values, results from previous studies have identified significant morbidity and mortality risks associated with hyperphosphatemia and hypercalcemia.[3-6,10-14] Because there are no generic alternatives to sevelamer hydrochloride, its use in this population and the impact of cost-sharing on adherence could have implications in the current healthcare environment.

The impact of sevelamer adherence on health plan resource utilization and total healthcare costs is an area for further research. Medicare+Choice beneficiaries with a capped annual drug benefit were found to have higher odds of nonadherence to antihypertensive, lipid-lowering, and diabetes medications (30%, 27%, 33%, respec-

Table 5 Characteristics Associated with Discontinuation of Sevelamer

Variable characteristics	2003 Adjusted odds ratios (95% CI)	2004 Adjusted odds ratios (95% CI)
Noncapped benefit referent	0.50 (0.20-1.27)	1.31 (0.41-4.16)
No parathyroidectomy referent	1.83 (0.54-6.18)	0.48 (0.07-3.16)
Continuous number of medications	0.98 (0.92-1.04)	1.00 (0.95-1.05)
Continuous age at first dispensing	0.99 (0.96-1.02)	1.01 (0.99-1.04)
Male referent	0.99 (0.44-2.19)	1.21 (0.55-2.65)
No atrial fibrillation referent	2.36 (0.61-9.14)	0.73 (0.18-2.88)
No hypertension referent	1.13 (0.43-2.96)	1.16 (0.42-3.21)
No CHF referent	0.79 (0.29-2.18)	NA
No CAD referent	NA	0.69 (0.31-1.55)
No metoprolol or atenolol use referent	1.76 (0.75-4.10)	1.26 (0.54-2.94)
No calcimimetics use referent	NA	3.11 (1.09-8.86)
Corrected Ca × P product ≤55 mg^2/dL^2 referent	0.39 (0.14-1.08)	2.56 (0.90-7.24)
No concurrent calcium-based phosphate binder referent	1.63 (0.66-4.02)	1.54 (0.60-3.96)

Ca × P indicates calcium-phosphorus product; CAD, coronary artery disease; CHF, chronic heart failure; CI, confidence interval.

Table 6 Clinical Marker Differences between Capped/Noncapped Groups

	2003					2004				
	Capped (n = 32)		Noncapped (n = 60)			Capped (n = 20)		Noncapped (n = 96)		
Characteristic	Median	(5th, 95th percentile)	Median	(5th, 95th percentile)	*P*	Median	(5th, 95th percentile)	Median	(5th, 95th percentile)	*P*
Corrected calcium values	9.7	(8.5, 10.8)	9.6	(8.0, 10.7)	.022	9.7	(8.4, 10.7)	9.5	(8.2, 10.5)	.003
Serum phosphorus values	5.5	(3.3, 7.8)	5.1	(3.4, 8.1)	.015	4.8	(3.0, 7.5)	4.9	(3.2, 7.9)	.097
Corrected calcium-phosphorus product	53.5	(30.9, 74.9)	48.8	(31.9, 74.7)	<.001	45.6	(28.8, 73.7)	46.5	(30.6, 74.0)	.433
Intact PTH values	299.5	(53.5, 1603.5)	300	(90.0, 1003.0)	.089	391	(100, 2186)	421	(98, 1449)	.369

PTH indicates parathyroid hormone.

tively).[25] Furthermore, patients with a capped benefit were more likely to have elevated systolic blood pressure (OR, 1.05; 95% CI, 1.00-1.09), LDL cholesterol (OR, 1.13; 95% CI, 1.03-1.25), and glycosylated hemoglobin (OR, 1.23; 95% CI, 1.03-1.46).[25] Finally, patients with a capped benefit had 28% lower pharmacy costs, 4% lower office visit costs, but 13% higher hospital costs and 9% higher emergency department costs.[25]

Sokol and colleagues examined the relationship between medication adherence for diabetes, hypertension, dyslipidemia, and CHF on the risk of hospitalizations and total healthcare expenditures.[38] Using diabetes as an example, they found that diabetic patients with adherence levels between 80% and 100% had a 13% risk of hospitalizations compared with 26% risk for those with adherence levels <40%. In patients with schizophrenia, 17% of adherent patients (>80% adherence) had a psychiatric hospitalization compared with 30% of nonadherent patients (<80% adherence).[39] In another study of patients with type 2 diabetes, adherence remained the strongest predictor for annual healthcare costs, where a decrease of between 8.6% and 28.9% was observed for every 10% increase in adherence.[40] Therefore, nonadherence has been associated with greater utilization of high-cost drivers of healthcare expenditures, such as inpatient visits and emergency department visits, which ultimately results in increased medical costs and the subsequent economic implications of medication nonadherence.

What are the implications of the lower adherence for sevelamer we found in our study on overall healthcare utilization and costs? It was beyond the scope of our study to directly examine this impact, but we conducted an estimation of the impact of lower adherence on total healthcare costs for patients with ESRD using published literature estimates for patients with diabetes who could be at risk for chronic kidney disease and ESRD.

The recent US Renal Data System (USRDS) reported an overall 50% change in new ESRD cases due to diabetes between 1996 and 2006.[36] Balkrishnan and colleagues found that a 10% decrease in medication adherence for diabetes can lead to an 8.6% to 28.9% increase in total healthcare costs.[40] We found that in 2003, patients with ESRD with a capped benefit had 27% lower adherence compared with those without a noncapped benefit. In 2004, those with a capped benefit had 33% lower adherence compared with those with a noncapped benefit. The USRDS 2008 annual data report for ESRD show that the per-member per-month (PMPM) cost of treating a patient with ESRD under Medicare in 2006 was $6266.[36] Moreover, Medicare expenditures were approaching $72,000 per patient annually in 2006 and inpatient/outpatient costs of $4300 PMPM for patients with ESRD.[36]

Using the conservative estimate of 8.6%[40] to extrapolate the impact of reduced adherence for sevelamer on healthcare costs, we can estimate that in 2003, patients with a capped benefit taking sevelamer potentially could have had 2.7-fold greater healthcare costs or a potential increase of $1454 PMPM in healthcare costs compared with patients with a noncapped benefit in 2003. Using the high-end estimate of 28.9%, we can estimate that patients taking sevelamer with a capped benefit could potentially experience an increase of $4889 PMPM in healthcare costs compared with patients with a noncapped benefit. Similarly, in 2004 the conservative estimate can potentially yield an increase of $1778 PMPM in total healthcare costs for

patients who were taking sevelamer with a capped benefit compared with those with a noncapped benefit. The high-end estimate can potentially yield an increase of $5975 PMPM in total healthcare costs in 2004 for patients taking sevelamer with a capped benefit compared with a noncapped benefit.

What are the implications of our findings for the Medicare Part D benefit? Using the Medicare Current Beneficiary Survey data between 1997 and 2001, Patel and Davis estimate that under the current Part D benefit, patients with ESRD will have mean annual OOP drug costs that are twice those of non-ESRD Medicare patients ($2329 vs $1331, respectively).[41] Approximately 54% of the patients with ESRD were taking more than 10 medications, and the majority of patients with ESRD reached the benefit gap (70% vs 43%, respectively) and the catastrophic coverage (39% vs 14%, respectively).[41] Patients with ESRD approached the benefit gap and catastrophic coverage earlier (June vs July and July vs September, respectively).[41] With a majority of patients with ESRD expected to reach prescription drug coverage limits by midyear and have significant OOP costs, our findings provide evidence of a negative impact of increased cost-sharing on sevelamer adherence.

Limitations

The small sample size was a limitation of this study, which may limit the generalizability of the findings, although the characteristics of the patients examined are similar to national estimates.[36] We compared retirees to Medicare members in this study and were unable to measure important variables, such as income, that could affect the ability to purchase prescription medications. It is possible that the retiree population in the noncapped group had higher income levels than the Medicare beneficiaries in the capped group, which might have influenced their adherence behavior as well.

We were also not able to measure whether the impact of a potential selection bias of patients with ESRD in a Medicare+Choice plan versus retirees in an employer-sponsored plan influenced the use of sevelamer.

Conclusion

Our pilot study revealed that patients with ESRD taking sevelamer under a capped benefit for brand-name coverage had lower levels of adherence compared with those who did not face such a restriction. These results provide preliminary evidence of how ESRD beneficiaries may fare under the current Part D benefit. With escalating inpatient and outpatient costs for patients with ESRD, research on medication adherence and its impact on healthcare costs will be beneficial. ■

Disclosure Statement

Dr Korner is currently an employee at Roche Pharmaceuticals.

References

1. Moe SM, Sprague AM. Mineral and bone disorders in chronic kidney disease. In: Brenner BM. *Brenner & Rector's The Kidney*. Philadelphia, PA: Saunders Elsevier; 2008.
2. Delmez JA, Slatopolsky E. Hyperphosphatemia: its consequences and treatment in patients with chronic renal disease. *Am J Kidney Dis*. 1992; 4:303-317.
3. Ganesh SK, Stack AG, Levin NW, et al. Association of elevated serum PO(4), Ca × PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*. 2001;12:2131-2138.
4. Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004; 15:2208-2218.
5. Block GA, Danese M, Kim K, et al. Elevated PTH and Ca × P levels are associated with increased hospitalization in hemodialysis patients. *Am J Kidney Dis*. 2003;41:A3. Abstract 15.
6. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium × phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31: 607-617.
7. Saran R, Bragg-Gresham JL, Rayner HC, et al. Nonadherence in hemodialysis: associations with mortality, hospitalization, and practice patterns in the DOPPS. *Kidney Int*. 2003;64:254-262.
8. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42(4 suppl 3):S1-S201.
9. Bleyer AJ, Burke SK, Dillon M, et al. A comparison of the calcium-free phosphate binder sevelamer hydrochloride with calcium acetate in the treatment of hyperphosphatemia in hemodialysis patients. *Am J Kidney Dis*. 1999;33:694-701.
10. Block GA, Klassen P, Danese M, et al. Relationship between serum calcium and mortality risk in hemodialysis patients. *Am J Kidney Dis*. 2003;41:A3. Abstract 16.
11. Chertow GM, Burke SK, Raggi P, for the Treat to Goal Working Group. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int*. 2002;62:245-252.
12. Goldberg DI, Dillon MA, Slatopolsky EA, et al. Effect of RenaGel, a non-absorbed, calcium- and aluminum-free phosphate binder, on serum phosphorus, calcium, and intact parathyroid hormone in end-stage renal disease patients. *Nephrol Dial Transplant*. 1998;13:2303-2310.
13. Slatopolsky EA, Burke SK, Dillon MA; the RenaGel Study Group. RenaGel, a nonabsorbed calcium- and aluminum-free phosphate binder, lowers phosphorus and parathyroid hormone. *Kidney Int*. 1999;55:299-307.
14. Chertow GM. Slowing the progression of vascular calcification in hemodialysis. *J Am Soc Nephrol*. 2003;14(9 suppl 4):S310-S314.
15. White CA, Jaffery J, Magner P. Cost of applying the K/DOQI guidelines for bone metabolism and disease to a cohort of chronic hemodialysis patients. *Kidney Int*. 2007;71:312-317.
16. Goodman WG. Medical management of secondary hyperparathyroidism in chronic renal failure. *Nephrol Dial Transplant*. 2003;18(suppl 3):iii2-iii8.
17. Amin N. The impact of improved phosphorus control: use of sevelamer hydrochloride in patients with chronic renal failure. *Nephrol Dial Transplant*. 2002;17:340-345.
18. *2003 Drug Topics Red Book*. Montvale, NJ: Medical Economics; 2003.
19. *2004 Drug Topics Red Book*. Montvale, NJ: Medical Economics; 2004.
20. Collins AJ, St. Peter WL, Dalleska FW, et al. Hospitalization risks between Renagel phosphate binder treated and non-Renagel treated patients. *Clin Nephrol*. 2000;54:334-341.
21. Loghman-Adham M. Medication noncompliance in patients with chronic disease: issues in dialysis and renal transplantation. *Am J Manag Care*. 2003;9:155-171.
22. Bame SI, Petersen N, Wray NP. Variation in hemodialysis patient compliance according to demographic characteristics. *Soc Sci Med*. 1993; 37:1035-1043.
23. Cleary DJ, Matzke GR, Alexander AC, Joy MS. Medication knowledge and compliance among patients receiving long-term dialysis. *Am J Health Syst Pharm*. 1995;52:1895-1900.

Continued

24. Hirth RA, Greer SL, Albert JM, et al. Out of pocket spending and medication adherence among dialysis patients in 12 countries. *Health Aff (Millwood)*. 2008;27:89-102.
25. Hsu J, Price M, Huang J, et al. Unintended consequences of caps on Medicare drug benefits. *N Engl J Med*. 2006;354:2349-2359.
26. Tamblyn R, Laprise R, Hanley JA, et al. Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *JAMA*. 2001;285:421-429.
27. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med*. 2006;166:1836-1841.
28. Patel BV, Remigio-Baker RA, Thiebaud P, et al. Improved persistence and adherence to diuretic fixed-dose combination therapy compared to diuretic monotherapy. *BMC Fam Pract*. 2008;9:61.
29. Doshi JA, Zhu J, Lee BY, et al. Impact of a prescription copayment increase on lipid-lowering medication adherence in veterans. *Circulation*. 2009;119:390-397.
30. The Pharmacy Quality Alliance. Proportion of days covered: antidepressant continuation phase. www.pqaalliance.org/files/Nov2008MeetingMaterials/MENTALHEALTHAntidepressContinuationPDCMeasureConcept.doc. Accessed February 20, 2009.
31. Centers for Medicare & Medicaid Services. Medicare Part D benefit parameters for standard benefit: annual adjustments for 2007. May 22, 2006. www.cms.hhs.gov/MedicareAdvtgSpecRateStats/Downloads/2007_Part_D_Parameter_Update.pdf. Accessed September 8, 2009.
32. Centers for Medicare & Medicaid Services. Notification of changes in Medicare Part D payment for calendar year 2008. www.cms.hhs.gov/MedicareAdvtgSpecRateStats/Downloads/PartDannouncement2008.pdf. April 2, 2007. Accessed September 8, 2009.
33. Biotechnology Industry Organization. Medicare Part D plans deliver significant savings on innovative, breakthrough medicines. www.bio.org/healthcare/medicare/BIOPricingSurvey.pdf. Accessed February 20, 2009.
34. Nayeem AI, Chertow GM. Lessons for Medicare Part D in the hemodialysis community. *BMC Nephrol*. 2006;7:11.
35. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159:702-706.
36. US Renal Data System. USRDS 2008 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. 2008. www.usrds.org/2008/pdf/V2_11_2008.pdf. Accessed January 21, 2009.
37. Karamanidou C, Clatworthy J, Weinman J, Horne R. A systematic review of the prevalence and determinants of nonadherence to phosphate binding medication in patients with end-stage renal disease. *BMC Nephrol*. 2008;9:2.
38. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare costs. *Med Care*. 2005;43:521-530.
39. Svarstad BL, Shireman TI, Sweeney JK. Using drug claims data to assess the relationship of medication adherence with hospitalization and costs. *Psychiatr Serv*. 2001;52:805-811.
40. Balkrishnan R, Rajagopalan R, Camacho FT, et al. Predictors of medication adherence and associated health care costs in an older population with type 2 diabetes mellitus. *Clin Ther*. 2002;25:2958-2971.
41. Patel UD, Davis MM. Falling into the doughnut hole: drug spending among beneficiaries with end-stage renal disease under Medicare Part D plans. *J Am Soc Nephrol*. 2006;17:2546-2553.

STAKEHOLDER PERSPECTIVE

Balancing Horizontal and Vertical Equity within Managed Health Plans Drug Benefit

PHARMACY/MEDICAL DIRECTORS: This study by Bhardwaja and colleagues once again highlights effects of prescription benefit coverage limitations on medication adherence in managed care drug programs. Providing coverage for beneficiaries reflects horizontal equity in that coverage is available for many members within a plan. Subsequently, very difficult decisions must be made concerning vertical equity—what will the scope of the benefit be for varying beneficiaries? Standardizing care coverage at different levels is a challenge for those involved in benefit design. Through a capped drug benefit, more coverage may be available for a broad base of enrollees, but such a capped benefit as was shown in this study decreased patients' compliance, which can lead to downstream costs that result from the negated beneficial aspect of enhanced compliance.

This study preceded the implementation of the Medicare Part D program, a market-based model of a government-subsidized health insurance program component that began on January 1, 2006. This program also provides a capped benefit with the coverage gap (doughnut hole). During 2006-2009, the median Medicare Part D premiums paid by beneficiaries increased by 35%; between 2008 and 2009 alone, premiums increased by 17%.[1] Cost-sharing requirements for recipients also increased by 35% over the 3-year period.[1]

The release of the latest Medicare Annual Report indicates that the Medicare hospital insurance (HI) trust fund is projected to be exhausted by the year 2017.[2] The annual updating report from 1 year ago indicated solvency of the HI trust fund through 2019, so in a 1-year period, a 2-year decrease has now been projected. Medicare Part D (and Part B) is funded through a supplementary medical insurance (SMI) fund, which is separate from HI, and SMI is projected to be solvent over the same time period. However, the state of the economy, increased demand for services, and looming healthcare reform could change the SMI metrics very quickly. How these economic challenges within the cacophony of the debates about healthcare reform influence drug benefit design programs will be important to observe in the coming months and years.

References

1. Hargrave E, Haodley J, Cubanski J, Neuman T. *New Analysis Reveals Rising Costs for Medicare Part D Enrollees Over Time*. *Washington*, DC: Kaiser Family Foundation. www.kff.org/medicare/upload/7917.pdf. Accessed June 11, 2009.
2. Centers for Medicare & Medicaid Services. *2009 Annual Report of the Boards of Trustees of the Federal Hospital Insurance and Federal Supplementary Medical Insurance Trust Funds*. www.cms.hhs.gov/reportstrustfunds/downloads/tr2009.pdf. May 2009. Accessed June 18, 2009.

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