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Cost-Effectiveness of Lanthanum Carbonate in the Treatment of Hyperphosphatemia in Dialysis Patients: A Canadian Payer Perspective

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ABSTRACT

Background: Hyperphosphatemia is a common and potentially harmful condition in patients with end-stage kidney disease. In Canada, first-line treatment of hyperphosphatemia consists primarily of calcium carbonate (CC). Lanthanum carbonate (LC) and sevelamer hydrochloride (SH) are non–calcium phosphate binders that have been used as second-line therapy in patients intolerant of or not responsive to CC.

Objectives: The primary objective of the present study was to assess the costs and clinical benefits of second-line use of LC after therapy failure with CC in patients receiving dialysis, from a Canadian payer perspective. The secondary objective was to perform an economic comparison between second-line LC therapy and second-line SH therapy, from a Canadian payer perspective. Short-term outcomes were treatment response and cost per additional responder, and long-term outcomes were survival, number of all-cause hospitalizations, and quality of life.

Methods: A cost-effectiveness Markov model was populated with simulated cohorts of 1000 patients receiving incident dialysis, followed life-long. Patients not responsive to CC with a serum phosphate concentration >1.78 mmol/L (>5.5 mg/dL) received a trial regimen with LC. Patients not responsive to LC returned to CC therapy. Patient data from a randomized controlled trial of 800 patients receiving dialysis were used. Extensive (probabilistic) sensitivity analyses were performed. When available, model parameters were based on Canadian data or from a Canadian perspective. All costs are in 2010 Canadian dollars (C$).

Results: Results of the model estimated that in patients responsive to second-line LC therapy, survival increased, on average, 0.44 years (95% confidence interval [CI], 0.35–0.54) per patient when compared with continued CC therapy. The mean (range) costs per patient in the first year of treatment with LC was C$2600 (C$2400–C$2800). Over patients' lifetimes, the second-line LC strategy resulted in a gain of 48.8 (37.1–61.3) life-years and 29.3 (21.4–38.1) quality-adjusted life-years (QALYs). The cost-effectiveness of the second-line LC strategy was C$7900 (C$1800–C$14,600) per life-year and C$13,200 (C$3000–C$25,100) per QALY gained. Most sensitivity analyses did not change the cost-effectiveness outcomes; however, including unrelated future costs raised the incremental cost-effectiveness ratio to C$159,500 (95% confidence interval, C$133,300–C$191,600) per QALY gained. Compared with second-line SH therapy, second-line LC therapy had similar effectiveness and was 23% less expensive.

Conclusions: Second-line treatment with LC is cost-effective in the treatment of end-stage kidney disease in patients with hyperphosphatemia, from a Canadian payer perspective. Second-line treatment with LC is less expensive, with similar effectiveness as second-line treatment with SH. The primary limitation of health economic evaluations of phosphate binders is the relative scarcity of clinical data on the association between phosphate concentration and

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long-term outcome. (*Clin Ther*. 2012;34:1531–1543)

Key words: Calcium carbonate, Cost-effectiveness, Dialysis, Hyperphosphatemia, Lanthanum carbonate, Sevelamer hydrochloride.

INTRODUCTION

End-stage kidney disease (ESKD, also known as chronic kidney disease stage 5) is, among other derangements, characterized by reduced or absent ability of the kidneys to regulate mineral metabolism. In Canada, ESKD is a leading cause of morbidity and mortality, with more than 36,000 patients having ESKD at the end of 2008, an increase of 57% over the previous 10 years.[1] Health care costs for ESKD were estimated to exceed Canadian dollars [C$]55,000 (US$34,400) per patient per year in 2002, with total expenditures for ESKD amounting to 1.2% of the total health care budget. Although kidney transplantation is the most common form of solid-organ replacement,[1] most patients with ESKD rely on dialysis as artificial replacement of lost kidney function. Despite dietary advice to restrict phosphate intake, and as a result of conventional dialysis therapy, the reduced ability of the kidneys to excrete serum phosphate (SP) leads to hyperphosphatemia in most patients.[2] Furthermore, dysregulation of calcium phosphate metabolism can lead to secondary hyperparathyroidism. Secondary hyperparathyroidism and hyperphosphatemia increase the risk of bone disorders, and are associated with a higher prevalence of cardiovascular diseases.[3] Large epidemiologic studies have demonstrated that elevated SP concentration is associated with increased mortality[4–6] and hospitalizations [5,7] in patients with ESKD.

The Canadian Society of Nephrology emphasizes the importance of adequate phosphate control in patients receiving dialysis.[8] Consequently, Canadian and international clinical guidelines recommend that SP concentration be maintained within the reference range.[8,9] Dietary management is usually not sufficient to control hyperphosphatemia, and most patients require treatment with oral phosphate binders.[10] In Canada, first-line treatment of hyperphosphatemia consists primarily of calcium-based phosphate binders, in particular, calcium carbonate (CC).[11,12] However, large or improperly administered calcium intake may lead to hypercalcemia, and may be associated with an increased risk of vascular calcification,[13] adverse effects less frequently seen when non–calcium phosphate binders are used exclusively.[14–16] Furthermore, not all patients respond adequately to calcium-based phosphate binders.

Lanthanum carbonate (LC) is a non–calcium-based phosphate binder that is licensed in several countries for treatment of hyperphosphatemia in patients with ESKD receiving dialysis[17–19] and for pre-dialysis stages of kidney disease in several countries; LC has not been licensed in Canada for use in patients with pre-dialysis stages of ESKD.[20] LC has been used in clinical practice in many countries as second-line treatment in patients intolerant of or not responsive to calcium-based binders.[21,22]

The cost-effectiveness of LC as a second-line treatment of hyperphosphatemia in dialysis patients has been demonstrated from UK, US, and Japanese health care payer perspectives.[22–24] The cost-effectiveness of non–calcium phosphate binders has also been evaluated from a Canadian perspective,[25,26] but not explicitly as second-line treatment in patients who have inadequately responded to a calcium binder. Because of relative cost reasons, second-line treatment represents the most likely positioning of non–calcium phosphate binders in clinical practice. Hence, the primary objective of the present study was to assess the potential costs and clinical benefits of second-line use of LC in dialysis patients with hyperphosphatemia compared with a strategy of continued calcium-binder treatment. The analysis was conducted from a Canadian payer perspective. Both short-term (treatment response) and long-term (survival, hospitalizations, and quality of life [QoL]) outcomes were explored. A further objective was to perform an economic comparison of LC and sevelamer hydrochloride (SH), an alternative non–calcium phosphate binder, in second-line use. This has previously been performed from a US payer perspective,[24] but not using Canadian-specific costs and population data.

METHODS

Economic Model

A cost-effectiveness model developed in Excel 2010 (Microsoft Corp, Redmond, Washington) was used to estimate the costs and clinical benefits of second-line LC in patients receiving dialysis, from a Canadian health care payer perspective. This was based on a published model developed using a UK health care payer perspective.[27] The model consisted of a decision tree

analysis with time-dependent Markov modeling techniques used to follow a cohort of 1000 patients receiving incident dialysis until death. Markov modeling is a commonly used technique in decision analysis to handle the complexity of multiple interconnective possible long-term consequences. The health states in the Markov model were dialysis and death; return to a pre-dialysis state was not allowed. The number of patients in each health state was determined by yearly cycles, and a half-cycle correction was applied. Costs and health effects were discounted at an annual rate in line with standard Canadian guidelines.[28] The primary comparison consisted of an assessment of the cost-effectiveness of second-line use of LC in dialysis patients with hyperphosphatemia not adequately responding to first-line CC, compared with the continued use of CC regardless of treatment response. Response to LC was evaluated during an 8-week trial, and in patients not responsive after this time, treatment was reverted to CC. Treatment response was defined as achieving a target SP ≤1.78 mmol/L (≤5.5 mg/dL) in patients with a baseline SP concentration exceeding this. On the basis of this short-term clinical outcome, the incremental direct health care cost in the first treatment year per additional responder for the LC strategy was determined. The analysis included assessment of long-term clinical outcomes associated with SP reduction including death, all-cause hospitalizations (primarily cardiovascular and fracture-related hospitalizations[5]), and QoL. This enabled a derivation of the lifetime incremental cost per life-year gained and incremental cost per quality-adjusted life-year (QALY) gained using the second-line LC strategy. All economic outcomes were rounded to the nearest C$100.

In addition, a secondary comparison was performed to assess the use of second-line LC therapy versus second-line SH therapy, with the definition of second-line therapy being the same as in the primary comparison versus continued CC therapy. For this analysis, a cost-minimization approach was used that was based on assumption of the similar efficacy of LC and SH.[29,30] A dose relativity ratio between LC and SH of 2.7 (95% confidence interval [CI], 2.4–3.1) was applied, derived from two separate assessments of dose relativity combining the results of treat-to-target studies,[29,30] meaning 1 g LC has similar phosphate-binding capacity as 2.7 g SH. Rates of adverse events for both treatments were also assumed to be similar, on the basis of clinical trial data.[31]

Model Parameters

The clinical pathways for the decision tree and Markov model are shown in **Figure 1**. Where possible, parameters for target SP concentration, risks of death and hospitalization, QoL outcomes, adverse event effect, and cost variables were based on Canadian data. A summary of the key model parameters is given in **Table I**. At model entry, all patients had an SP concentration >1.78 mmol/L (>5.5 mg/dL). On the basis of Canadian and international guidelines, the target SP concentration that defined successful response to treatment was ≤1.78 mmol/L (≤5.5 mg/dL),[8,9] and a lower target SP concentration of ≤1.47 mmol/L (≤4.6 mg/dL) was explored in sensitivity analyses. The clinical pathway and parameters for the Canadian model were discussed and validated with four Canadian nephrologists.

Clinical Efficacy

For the primary comparison, efficacy parameters were based on patient-level data from a Phase III, randomized, active comparator-controlled trial (RCT) of LC versus CC in 800 patients receiving hemodialysis.[16] At the end of the RCT phase, 65.8% and 63.9% of patients achieved SP control with LC and CC, respectively. More patients who received CC experienced hypercalcemia (20.2% vs 0.4%). The double-blind phase of the RCT was followed by a 6-month open-label extension phase in which all patients received LC.[32] To provide a clinically relevant assessment of the use of second-line LC therapy, patients from the clinical trial were selected for inclusion in the economic model if they were randomized to receive CC, had an SP concentration >1.78 mmol/L (>5.5 mg/dL) at the end of the RCT double-blind phase, and were given LC in the open-label phase. Therefore, data on relative treatment effect was available from the trial for 257 patients treated with first-line CC and 123 patients receiving second-line LC. Long-term LC response was modeled using the patient-level data, and has been described in detail elsewhere.[23]

On the basis of evidence from epidemiologic datasets, associations between SP concentration and death[5] and hospitalizations[5,7] were included in the Markov model. Baseline expected survival was based on a random sample of more than 18,000 Canadian patients with ESKD registered in the Canadian Organ Replacement Registry.[33] The baseline all-cause hospitalization rate was derived from Canadian observational data.[34,35] In the RCT, vom-

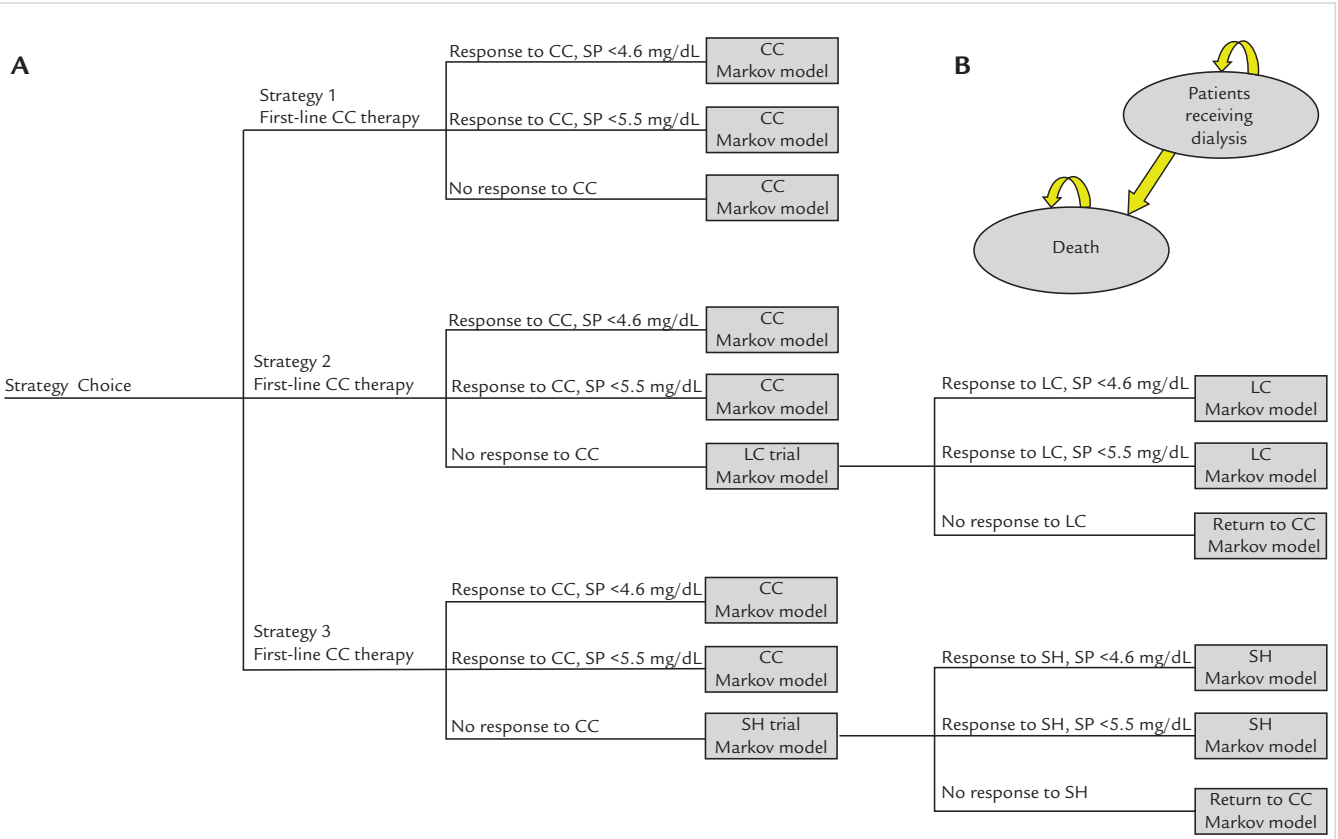

Figure 1. (A) Decision analytical model. (B) Markov model.

iting was the only adverse event, with a significantly increased occurrence in the LC arm;[16] the duration of this adverse event was estimated to be 7 days.[23,27] During this period, patients were prescribed an antiemetic drug (assumed to be domperidone, 40 mg/d). The primary and most obvious adverse effect of calcium-based phosphate binders is hypercalcemia,[5,36] which is not apparent with non–calcium binders.[16] However, because of lack of available evidence,[37] the influence of hypercalcemic events was not included in the model.

Costs and Utilities

A Canadian payer perspective was adopted for cost estimates, which are reported in 2010 C$. Drug costs were based on the Canadian Formulary drug prices.[38] For the second-line LC model, LC and CC dosages were based on the mean daily dosage from the clinical trial,[16] and SH dosages were based on the dose relativity ratio between LC and SH.[29,30] Hospitalization and dialysis costs were derived from Canadian costing studies in nearly 300 patients undergoing various dialysis methods, followed prospectively for at least 1 year.[34,39] Additional dialysis costs in gained life-years were classified as "unrelated future costs," ie, costs associated with dialysis that are not influenced by use of phosphate binders.[40,41] These costs were excluded from the base-case analysis following Canadian Agency for Drugs and Technologies in Health recommendations on valuing resource use and costs.[28]

For assessment of QALYs, the health-related QoL must be measured as utilities.[28] A utility for dialysis in Canadian patients has been reported to be 0.61, based on the EuroQoL EQ-5D questionnaire.[42] A utility decrement of 0.14 was assumed in patients who experienced a vomiting episode as an adverse event of treatment for the duration of this adverse event, based on published estimates.[43] Furthermore, a hospitalization episode was assumed to have a disutility value of 0.19 for the duration of hospitalization, estimated to be 9.3 days on average.[34] These utility decrements were applied cumulatively.

Table I. Model parameters.

Variable	Value (95% CI)	Source
Clinical pathway, mmol/L		
Treatment initiation level	>1.78	Shire[44]
Target level	≤1.78	K/DOQI[45]
Drug efficacy, %		
First-line response rate to CC	62.2 (59.0–65.4)	Hutchison et al[16]
Second-line response rate to CC	44.4 (40.0–48.5)	Hutchison et al[16]
Long-term response to LC	λ = 0.55 (0.45–0.63)	Hutchison et al[16]
	γ = 0.92 (0.78–1.05)	
Mortality		
Baseline yearly mortality, %	13.0 (12.3–14.3)	CORR[1]
RR of mortality by SP band, mmol/L		Block et al[5]
≤0.97	1.10 (0.96–1.24)	
0.98–1.29	1.00 (0.93–1.07)	
1.30–1.45	1.00 (1.00–1.00)	
1.46–1.61	1.00 (1.00–1.00)	
1.62–1.78	1.07 (1.01–1.14)	
1.79–1.94	1.07 (1.01–1.14)	
1.95–2.26	1.25 (1.17–1.34)	
2.26–2.58	1.43 (1.31–1.54)	
2.59–2.91	1.67 (1.51–1.86)	
≥2.92	2.02 (1.76–2.27)	
Hospitalizations		
Baseline hospitalization per year	2.49 (2.13–2.83)	Goeree et al[34]; Murphy et al[35];
RR of hospitalization by SP band, mmol/L		Block et al[5]
≤0.97	1.00 (0.80–1.20)	
0.98–1.29	1.00 (0.80–1.20)	
1.30–1.45	1.00 (1.00–1.00)	
1.46–1.61	1.00 (1.00–1.00)	
1.62–1.78	1.04 (1.00–1.08)	
1.79–1.94	1.04 (1.00–1.08)	
1.95–2.26	1.09 (1.00–1.18)	
2.26–2.58	1.18 (1.00–1.36)	
2.59–2.91	1.20 (1.00–1.40)	
≥2.92	1.31 (1.00–1.62)	
Quality of life		
Utility of patients receiving dialysis	0.61 (0.52–0.69)	Manns et al[42]
Utility decrement during vomiting	0.14 (0.08–0.20)	Osoba et al[43]
Utility decrement during hospitalization	0.19 (0.14–0.24)	Rosenberger et al[46]; Shmueli et al[47]; Shmueli et al[48]

(continued)

Table 1 (continued).

Variable	Value (95% CI)	Source
Adverse events		
Increase in vomiting with LC and SH, %	7.2 (5.4–9.0)	Hutchison et al[16]; Sprague et al[31]
Duration of vomiting, d	7 (5.3–8.8)	Hutchison et al[16]
Duration of hospitalization, d	9.3 (6.9–11.6)	Murphy et al[35]
Drug dosage and cost		
Mean dose of LC, mg/d	1937 (1829–2045)	Hutchison et al[16]
Dose relativity of LC:CC	0.52 (0.45–0.58)	Wilson et al[29]; Daugirdas et al[30]
Dose relativity of LC:SH	2.70 (2.4–3.1)	
Drug price* of CC tablet		
500-mg	C$0.0252	Canadian Formulary[38]
750-mg	C$0.0322	
Annual cost	C$64	
Drug price of LC (Fosrenol†) tablet		
250-mg	C$1.03	Canadian Formulary[38]
500-mg	C$2.06	
750-mg	C$3.10	
1000-mg	C$4.11	
Annual cost	C$2913	
Drug price of SH (Renagel‡) tablet		Canadian Formulary[38]
800 mg	C$1.50	
Annual cost	C$3580	
Dialysis cost	C$67,738 (C$59,290–C$77,290)	Goeree et al[33]
Hospitalization cost (per incidence)	C$7973 (C$6430–C$9890)	Goeree et al[33]
Discounting rate, %	5	CADTH[28]

CADTH = Canadian Agency for Drugs and Technologies in Health; CC = calcium carbonate; CI = confidence interval; LC = lanthanum carbonate; RR = relative risk; SH = sevelamer hydrochloride; SP = serum phosphate.
*All costs are given in 2010 Canadian dollars (C$).
†Shire US, Inc, Wayne, Penn.
‡Genzyme Corp, Cambridge, Mass.

Sensitivity Analyses

For the primary comparison, sensitivity analyses were performed for all model parameters using probabilistic sensitivity analysis (10,000 iterations) to model joint parameter uncertainty, enabling calculation of 95% CIs.[46] The probability distributions chosen for the probabilistic sensitivity analysis were based on those recommended for health economic analysis,[49] and include distributions used for the UK evaluation of the cost-effectiveness of LC.[27] In addition, several scenario analyses were performed. A lower SP treatment target of ≤1.47 mmol/L (<4.6 mg/dL) was explored. Concomitant prescription of LC and CC was also explored, as suggested by Canadian clinical experts and the literature.[50,51] Other scenario analyses used different literature sources for various model parameters including baseline mortality[2] and hospitalization rate,[35] inclusion of unrelated future costs, and variations in model time horizon and discounting rates.

RESULTS

Primary Comparison

Of the total model cohort of 1000 patients receiving incident dialysis, 622 (62.2%) were estimated, on the basis of RCT data, to achieve target SP concentrations with CC therapy. In the other 378 patients (37.8%),

Table II. Cost-effectiveness of second-line LC therapy compared with continued use of CC.

Variable	Continuous CC Therapy	First-Line CC, Second-Line LC Therapy	Difference (95% CI)
No. of patients with hyperphosphatemia receiving incident dialysis	1000	1000	
Short-term outcomes			
First-line response to CC (No., %)	622 (62.2)	622 (62.2)	NA
Non-response to CC (No., %)	378 (37.8)	378 (37.8)	NA
Second-line response to LC (No., %)	NA	168 (44.4)	168
Treatment costs* in first year	C$58,000	C$497,000	C$439,000 (C$389,000–C$496,000)
Long-term outcomes			
Survival (y)	5489	5537	48.8 (37.1–61.3)
Quality of life (QALYs)	3284	3314	29.3 (21.4–38.1)
Drug costs	C$351,000	C$1,143,000	C$791,000 (C$670,000–C$945,000)
Hospitalization costs	C$403,000	C$0	–C$403,000 (–C$737,000–C$115,000)
Total costs	C$754,000	C$1,143,000	C$388,000 (C$75,000–C$714,000)
Cost-effectiveness			
Cost per additional responder			C$2600 (C$2500–C$2800)
Cost per life-year gained			C$7900 (C$1800–C$14,600)
Cost per QALY gained			C$13,200 (C$3000–C$25,100)

The commonly cited threshold (willingness to pay) for cost-effective treatments in Canada is $50,000 per QALY gained.
CC = calciium carbonate; CI = confidence interval; LC = lanthanum carbonate; NA = not applicable; QALY = quality-adjusted life-year.
*All costs are given in 2010 Canadian dollars (C$).

CC therapy failed, and they therefore received an 8-week trial of LC therapy. On the basis of the RCT data, response to the target SP concentration was achieved with second-line LC in 168 of 378 CC non-responders (44.4%). The main costs and clinical benefits were driven by these additional responders. In patients responsive to LC therapy, improved SP control increased survival on average 0.44 years (95% CI, 0.35–0.54) per patient when compared with continued treatment with CC. In the overall cohort of 1000 patients, the second-line LC strategy resulted in 48.8 life-years gained (95% CI, 37.1–61.3), corresponding to 29.3 additional QALYs (95% CI, 21.4–38.1).

The results for incremental first-year treatment costs per additional responder associated with the second-line LC strategy were C$2600 (95% CI, C$2400–C$2800). Over the lifetime horizon, the additional costs in the overall cohort of 1000 dialysis patients receiving second-line LC were C$388,000 (95% CI, C$87,000–C$692,000). The cost-effectiveness of the second-line LC strategy was C$7900 (C$1800–C$14,600) per life-year gained, and C$13,200 (95% CI, C$3,000–C$25,100) per QALY gained (**Table II**).

From the sensitivity analysis performed, the results were robust to most variations in model parameters (**Figures 2** and **3**). LC drug price and the QoL of dialysis patients were influential on the cost-effectiveness estimates. Several scenario analyses were explored, but did not substantially change the cost-effectiveness results for second-line LC therapy. However, when unrelated future costs were included, the additional high costs of dialysis raised the incremental cost-effectiveness ratio to C$159,500 (95% CI, C$133,300–C$191,600) per QALY gained. The cost-effectiveness acceptability curve was calculated for both the base-case analysis and the scenario analysis, in which unrelated future costs were included (**Figure 4**), clearly

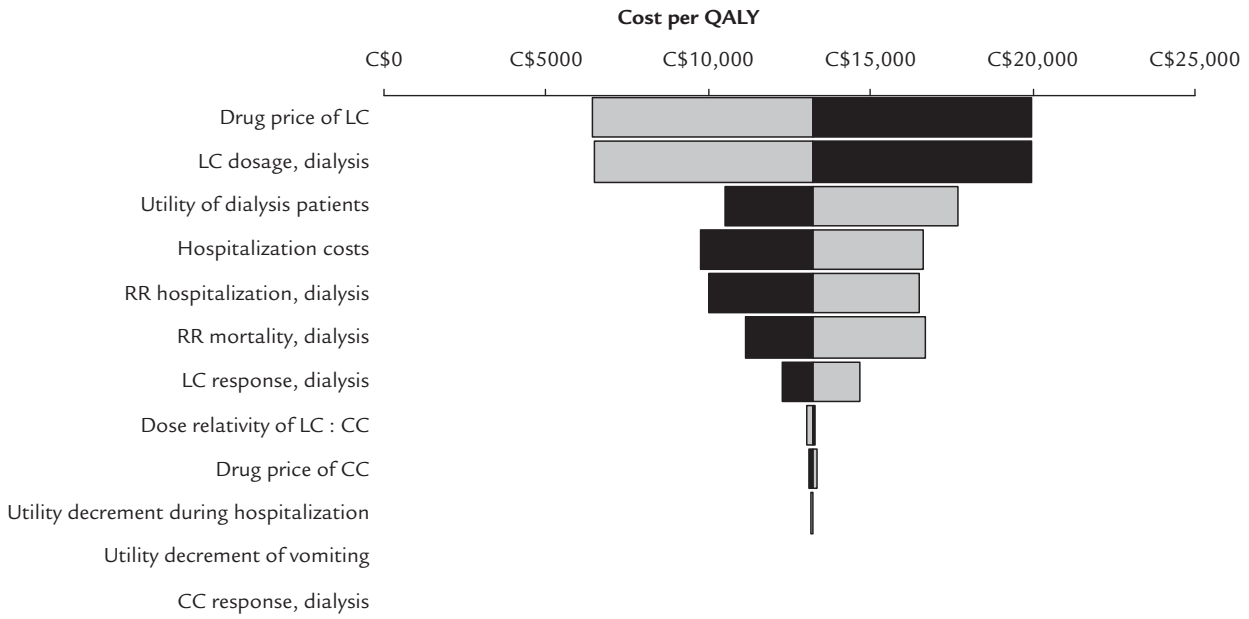

Figure 2. Sensitivity analysis shows the influence of ±25% change in model parameters on the cost-effectiveness of second-line LC treatment (black bars, +25%; gray bars, −25%). The commonly cited threshold (willingness to pay) for cost-effective treatments in Canada is C$50,000 per QALY gained. CC = calcium carbonate; LC = lanthanum carbonate; QALY = quality-adjusted life year; RR = relative risk.

showing the large influence of future unrelated costs on the cost-effectiveness of the treatment strategy.

Secondary Comparison

For the cost-minimization comparison of LC versus SH therapy, the average daily dose of LC in the clinical trial was 1937 mg, compared with 5234 mg for SH to achieve comparable efficacy, on the basis of absolute estimate of dose relativity. The resulting annual drug costs for LC were C$2900, compared with C$3600 for SH. Thus, second-line therapy with LC was associated with 23% lower cost than SH. Over patients' lifetimes, the treatment strategy using second-line therapy with LC was C$184,200 (95% CI, C$90,000–C$295,900) less costly than therapy using SH for the overall cohort of 1000 patients receiving incident dialysis.

DISCUSSION

The cost-effectiveness of non–calcium phosphate binders for treatment of hyperphosphatemia has previously been evaluated from a Canadian perspective as first-line treatment[25,26]; however, to date, use as second-line treatment in patients not responsive to calcium binders has not been evaluated. Inasmuch as calcium-binder drugs are relatively inexpensive and are currently the standard first-line treatment for hyperphosphatemia in Canada,[11,12] second-line use represents the most likely positioning in clinical practice for the non–calcium phosphate binders such as LC or SH. In the present economic evaluation, second-line treatment with LC was associated with higher drug costs over a patient's lifetime horizon, but also improved potential survival and QoL. As a result, the incremental cost-effectiveness ratio was well below the commonly accepted Canadian threshold (willingness to pay) of C$50,000 per QALY gained.[6,52–55] These results show the potential clinical benefits of improved SP control in terms of decreased mortality[4–6] and hospitalization rates.[5] The favorable value for money of second-line treatment with LC has also been found in previous economic evaluations in other countries (ie, UK, US, and Japanese payer perspectives).[22–24,27] In the first year of treatment, the total health care costs per additional responder patient achieving the SP targets were ~C$2600.

First-line treatment of hyperphosphatemia in clinical practice consists primarily of the use of calcium-based phosphate binders, primarily because of their

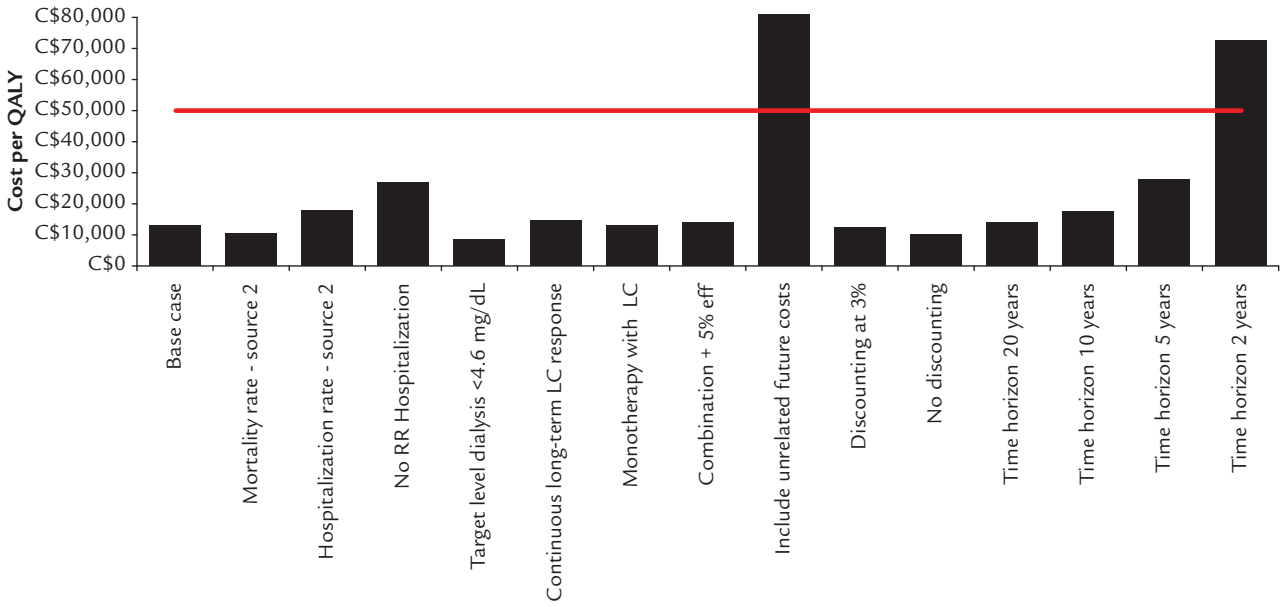

Figure 3. Scenario analyses show the influence of several clinical or methodologic changes on the cost-effectiveness of second-line LC treatment. The scenario "Include unrelated future costs" runs off the chart, value is C$159,500 per QALY gained. Red line denotes the commonly cited threshold (willingness to pay) for cost-effective treatments in Canada at C$50,000 per QALY gained. C$ = Canadian dollars; CC = calcium carbonate; LC = lanthanum carbonate; QALY = quality-adjusted life-year; RR = relative risk.

low cost. However, Clinical practice guidelines have recommended that daily calcium intake from phosphate binders should not exceed 1500 mg.[9] This economic evaluation supports the use of LC as a feasible second-line therapy in patients with ESKD in whom CC as first-line phosphate-binding therapy is failing, but also could represent a cost-effective alternative in patients who are intolerant of CC.

We compared treatment costs of second-line LC and second-line SH therapies. Pivotal to this analysis were data from two independent dose relativity studies.[29,30] The analysis showed that at dosages with similar phosphate-binding capacity, drug treatment costs for LC were ~23% lower than for SH. The favorable position of second-line LC compared with second-line SH therapy was also found in a recent economic analysis using a US payer perspective.[24]

Sensitivity and scenario analyses have demonstrated the robustness to reasonable variations in model parameters and assumptions. The only variation that resulted in a nonfavorable cost-effectiveness ratio was the inclusion of unrelated future dialysis costs, which are the costs of dialysis incurred by patients in the additional life-years they live but are not related to phosphate binder use.[42] The effect of this has also been reported in other economic evaluations of phosphate binders,[26,27] and can be explained in that dialysis itself is associated with a high cost per QALY gained. However, Canadian health economic guidelines recommend exclusion of future unrelated costs.[28]

The strengths of the present study include using patient-level data from the largest RCT with LC to enable accurate modeling of second-line treatment with LC. Further, the model parameters were based on Canadian data and perspective, increasing the relevance for Canadian clinical practice.[56] Furthermore, the model structure and parameters were based on a previously peer-reviewed model,[27] and were validated by Canadian clinicians.

The primary limitations of the present study are those common to health economic analyses, which include the use of intermediate end points, extrapolation over patients' lifetimes, and the need to combine various data sources.[49] A particular limitation is that the effects from a clinical trial with 6-month follow-up were extrapolated over patients' lifetime in the model. A direct association between SP concentrations attained over a short duration (6 months) and long-term outcomes has not been well established. However, sev-

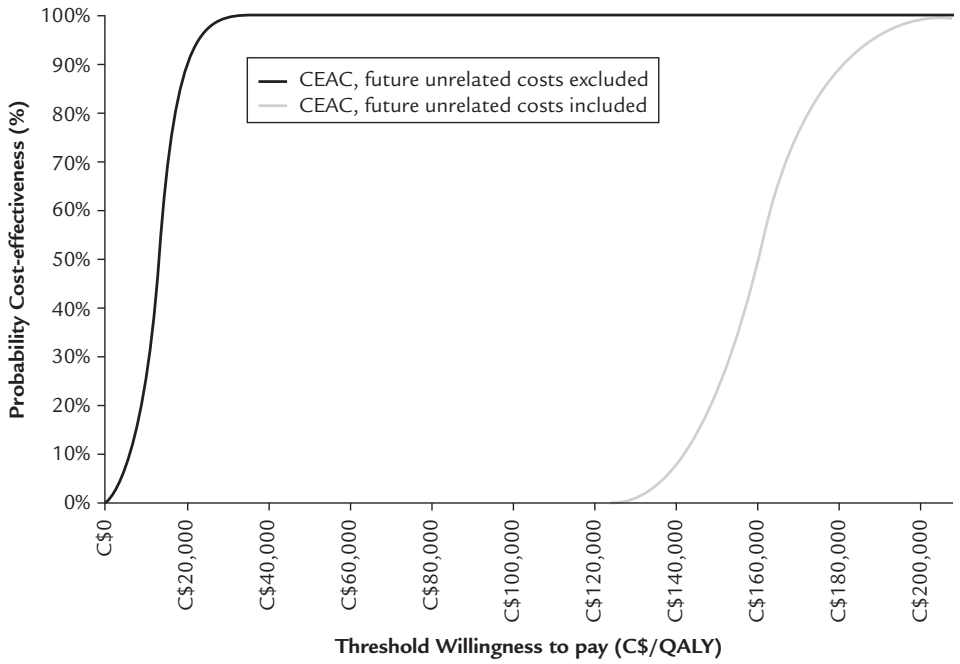

Figure 4. Cost-effectiveness acceptability curve (CEAC) of second-line LC treatment. Black line indicates future unrelated costs excluded; gray line indicates future unrelated costs included. C$ = Canadian dollars; QALY = quality-adjusted life-year.

eral clinical studies have now been published that confirm that, compared with no treatment, phosphate binders are independently associated with decreased mortality.[57] The utility decrement due to vomiting as an adverse event related to LC or SH therapy was based on a chemotherapy study.[43] This was a conservative estimate because specific data in populations with renal disease were unavailable; furthermore, the influence of this parameter on the cost-effectiveness outcomes was small. A further limitation is that it was not possible, because of lack of sufficient data, to include several other clinical benefits of LC therapy including the lower pill burden with LC compared with calcium binders and SH,[58,59] associated higher therapy adherence,[60] and lower risk of hypercalcemic events.[61] If taken into account, these factors might increase the clinical and economic outcomes and improve the cost-effectiveness of second-line therapy using LC.

CONCLUSIONS

This economic analysis has demonstrated that the use of LC as second-line therapy for hyperphosphatemia is cost-effective from a Canadian payer perspective. More patients will achieve SP concentrations in the recommended range with LC as a second-line treatment option. This improved SP control, in turn, was modeled to improve patient survival and reduce the number of hospitalizations. Although drug treatment costs are higher with LC than with CC, these are partly offset by reduced costs of hospitalization. Although the results were insensitive to changes in most model parameters, inclusion of unrelated future costs had a large influence on cost-effectiveness. The secondary comparison found that when treating to a target level of SP reduction in patients receiving dialysis, LC can achieve this target at a 23% lower drug cost than with SH. Cost-effectiveness evidence of the type presented herein is valuable for reimbursement and formulary decision making.

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All authors contributed to the design of the study. Dr. Vegter and Mr. Tolley programmed the model and drafted the report. All authors contributed to the data analysis, interpretation of the findings and reviewing draft versions of the report. All authors gave final approval to the manuscript.

CONFLICTS OF INTEREST

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