Research Artilce

iMedPub Journals
http://www.imedpub.com

Journal of Health & Medical Economics
ISSN 2471-9927

2016
Vol. 2 No. 1: 4

DOI: 10.21767/2471-9927.100010

Cost-minimization Analysis between Sevelamer and Lanthanum in Treating Hyperphosphatemia among Patients with End-stage Renal Disease in China

Li Yang[1], Seng Chuen Tan[2], Can Chen[2] and Xinya Li[1]

1 Peking University Health Science Centre, Beijing, China
2 IMS Health, Asia Pacific, Singapore

Corresponding Author: Seng Chuen Tan

IMS Health, Asia Pacific, Singapore.

sctan@sg.imshealth.com

Tel: 65 6412 7310

Citation: Yang L, Tan SC, Chen Can, Li X. Cost-minimization Analysis between Sevelamer and Lanthanum in Treating Hyperphosphatemia among Patients with End-stage Renal Disease in China. J Health Med Econ. 2016, 2:1.

Abstract

Background: Hyperphosphatemia is a great challenge for all countries, which contributes to vascular calcification and is associated with all-cause mortality for patients with chronic kidney disease. There are evidences showing the better efficacy in mortality, hospitalization of non-calcium based phosphate binders versus calcium-based phosphate binders. This study aims to provide scientific evidence on economic evaluation between two new non-calcium based phosphate binders, sevelamer and lanthanum, among end-stage renal disease patients in China through cost-minimization analysis from a patient perspective.

Methods: A cost-minimization analysis comparing sevelamer and lanthanum was conducted based on a review of current clinical evidence in treating hyperphosphatemia in China. The local unit costs, the equivalent dose ratios, estimated daily doses and survival extrapolation in published studies were applied.

Results: Our cost analysis indicates that sevelamer is likely to cost less than lanthanum in the local context of China with potential savings of up to approximately RMB 38,000 per patient over an estimated survival projection of 5.38 years for a dialysis patient with hyperphosphatemia.

Conclusion: For the treatment of hyperphosphatemia in end-stage renal disease patients in China, our analysis demonstrates sevelamer being likely a cost-saving option compared to lanthanum, both non-calcium based phosphate binders that provide more efficacious alternatives than calcium-based phosphate binders.

Keywords: Hyperphosphatemia; Disease burden; Phosphate binder; Sevelamer; Cost-minimization; China

Received: November 02, 2015; **Accepted:** November 19, 2015; **Published:** November 29, 2015

Introduction

Hyperphosphatemia is a common complication in end-stage renal disease (ESRD) in China with a prevalence of 57.4% in hemodialysis patients and 47.4% in peritoneal dialysis patients [1]. Due to the reduction in filtered phosphate from impaired glomerular filtration rates, serum phosphate level increases secretion of parathyroid hormone as a compensation, which leads to calcium phosphate release from the bone and therefore complications such as mineral and bone disorder and cardiovascular calcification [2].

In China, the guidance issued by national nephrology society suggests that serum phosphate level should be maintained between 1.13-1.78 mmol/L for ESRD patients with hyperphosphatemia [3]. However, 27.4% of hemodialysis patients and 25.0% of peritoneal dialysis patients with hyperphosphatemia were reported in a national dialysis survey not treated with any phosphorus binders [1]. Uncontrolled hyperphosphatemia contributes to the development of secondary hyperparathyroidism, renal osteodystrophy, vascular calcification, and a graded increase of all-cause mortality in dialysis patients [4-8]. Calcium-based binders, despite the

effectiveness in decreasing serum phosphate level, were reported potentially to increase the risk of hypercalcaemia therefore increase risk for vascular calcification and intact parathyroid hormone disorder [9]. Numerous studies demonstrated that the daily calcium intake was correlated with the condition of vascular calcification [10,11] which is a significant risk factor for and highly correlated with cardiovascular diseases and mortality [12,13]. In response to these concerns, both international [14] and local [3] guidelines recommend calcium-based binders are restricted for hyperphosphatemia in patients with persistent/ recurrent hypercalcaemia, calcification, persistently low PTH, and/or a dynamic bone disease. Newer treatment options such as non-calcium based binders including sevelamer and lanthanum are also recommended for hyperphosphatemia in patients with ESRD. The Dialysis Clinical Outcomes Revisited (DCOR) study demonstrated that patients assigned to sevelamer were found to have 15% risk decrease in length of hospital stay compared to patients assigned to calcium based binders [15]. In a recent meta-analysis, a significant lower risk of all-cause mortality by 12% was concluded for chronic kidney disease (CKD) patients treated with non-calcium based binders [16].

Non-calcium based phosphate binders such as sevelamer carbonate (Renvela®) and lanthanum carbonate (Fosenol®) have been available as self-pay items in China since 2013 and 2012 respectively. However, our review did not find any published economic analysis of non-calcium based phosphate binders for hyperphosphatemia in the local context of China. Both US and one Canada based cost studies concluded that the conversion from sevelamer to lanthanum was a potentially cost-saving or cost-effective strategy [17,18] for achieving similar serum phosphate reduction in patients with ESRD. A more recent cost-minimization analysis showed that conversion to lanthanum from sevelamer carbonate reduced drug costs and tablet burden in the event where the total daily dose of sevelamer was 5,600 mg or higher in the setting of the US [19]. It is worthwhile to note that as the unit costs and the average daily doses of both products may vary across different countries, any cost analysis and comparison between different products should be locally specific.

Clinical studies conducted in overseas have shown comparable efficacy for sevelamer and lanthanum in terms of serum phosphate and calcium control, and both are safe and well-tolerated in patients under hemodialysis [20,21]. Similar serum phosphate relative reduction was also observed in separate Chinese placebo controlled studies of sevelamer (-0.63 mmol/L) [22] and lanthanum (-0.48 mmol/L) [23]. Therefore, based on a conservative assumption of equivalent efficacy of both treatments, we performed a cost-minimization analysis to compare sevelamer and lanthanum in treating hyperphosphatemia among patients with ESRD in China.

Methods

Published international and local studies of non-calcium based phosphate binders were searched and reviewed. Research written in English or Chinese and published before June 2015 was identified using PubMed, CNKI, and Wanfang Med database searches. Assuming equivalent efficacy of both treatments, we conducted a Microsoft Excel based cost-minimization analysis between the two non-calcium based phosphate binders, sevelamer and lanthanum, among dialysis patients with hyperphosphatemia in the setting of China. Published clinical studies on equivalent dose ratios between sevelamer and lanthanum were searched and extensively reviewed. Exclusion criteria included crossover study of unidirectional design and high concomitant dose of calcium based phosphate binders with daily intake of 500 mg and above. Based on the findings in these studies, we estimated the likely therapeutically equivalent doses of the two binders in controlling and maintaining the recommended serum phosphate level among Chinese patients with dialysis. As both the products are not currently reimbursed by public payers, we conducted the analysis from a patient perspective. Published local unit drug prices were applied to estimate the daily cost of sevelamer and lanthanum. The published survival projection for the same patient population was referenced to complete the analysis on a lifetime horizon. Sensitivity analysis was conducted to evaluate the impact of projected survival duration. The analyses also conservatively assumed no difference in complication and hospitalization rates between the two binders. As such only the acquisition costs of these two drugs were considered in our analysis.

Results

Four clinical studies investigating equivalent dose ratio of sevelamer and lanthanum were identified. Sprague et al. compared the reduction of serum phosphorus through a crossover study of hemodialysis patients [21]. The primary analysis of data from this study suggests that at the doses compared, lanthanum carbonate (3,000 mg/day) and sevelamer hydrochloride (6,400 mg/day) are effective phosphate binders that reduce serum phosphorus to a similar degree. In a large cohort study of real world patients with ESRD, the overall mean sevelamer hydrochloride/ carbonate: lanthanum carbonate dose-relativity ratio of 2.27 (95% CI, 2.04 to 2.52) [24] was reported in Keith et al. The unidirectional switching study from lanthanum to sevelamer based on a post hoc analysis by Wilson et al. was excluded [25]. The Japanese study by Satoshi et al. was excluded for the average baseline calcium carbonate dose of greater than 500mg daily (1,790 mg) which also probably explains relatively lower daily sevelamer (2,971 ± 1,464 mg) and lanthanum doses (945 ± 449 mg) [26].

For the cost-minimization analysis, the equivalent dose ratios in both Sprague et al. (scenario 1) and Keith et al. (scenario 2) were therefore used to estimate the therapeutically equivalent average daily dose of sevelamer and lanthanum. In scenario 1, based on the equivalent dose ratio of sevelamer/lanthanum at 2.13 [21], the daily dose of sevelamer in Chinese patients was estimated at 4,392 mg by using the average dose of 2,062 mg lanthanum derived from an multi-center randomized controlled trial in China [23]. Given that the retail pharmacy prices of RMB 14.53 per tablet of Renvela® (sevelamer carbonate 800 mg) [27] and RMB 24.00 per tablet of Fosenol® (lanthanum carbonate 500 mg) [28], the daily drug costs were RMB 79.77 and RMB 98.98 respectively for sevelamer and lanthanum. This implies estimated daily cost difference of RMB 19.21 and therefore annual cost difference of RMB 7,012 as a potential total cost-saving for a patient treated

with sevelamer. In scenario 2, using a different dose-relativity ratio of 2.27, the daily drug cost of sevelamer (4,681 mg) was estimated at RMB 85.01 compared to RMB 98.98 for daily dose of lanthanum at 2,062 mg in China. Potential annual cost saving of RMB 5,099 was estimated in the same comparison remains despite smaller daily cost difference between the two non-calcium based binders.

A potential lifetime cost savings of RMB 37,725 and RMB 27,437 were estimated in the two scenarios respectively for a patient treated with sevelamer instead of lanthanum by applying the estimated cost differences to an expected life year of 5.38 years [28] that was projected in the cost-effectiveness analysis of lifetime horizon by Bernard et al. The average lifetime cost saving remains above RMB 20,000 for a sensitivity analysis of assuming a similar expected life year of 4.33 years as projected in a separate economic evaluation [29] (**Table 1**).

Discussion

Apart from health issues caused by disease, the medication and relevant healthcare costs are important concerns to healthcare system for all countries. In countries such as China, accessibility is a valid challenge for treatments which are available as fully self-pay items [30]. In addition, affordability is an important factor affecting adherence [31].

New generation phosphate binders, both sevelamer and lanthanum are now available in China. Published evidence has shown that non-calcium phosphate binders are efficacious and well tolerated for the treatment of hyperphosphatemia in hemodialysis and peritoneal-dialysis patients. Outcomes improvements such as reduced hospitalization rate and lower mortality risk were also demonstrated for non-calcium based phosphate binders such as sevelamer in comparison to calcium based phosphate binders [15,16].

Although non-calcium based phosphate binders are more costly than calcium based binders, their benefits in reducing hospitalization and mortality could be translated to economic benefits considering not only drug acquisition cost but also other medical costs in a cost-effectiveness analysis from both payer and societal perspectives for the local context in China. Overseas, a number of economic evaluations on non-calcium based phosphate binders for treatment of hyperphosphatemia have been published in the context of various countries by applying the relative risk data shown in relevant clinical studies or meta-analysis for different patient groups of interest [32-35]. For example, a cost-effectiveness analysis concluded that sevelamer offered good value for money compared with calcium-based binders for treatment of hyperphosphatemia among CKD patient on dialysis from the perspective of the National Health Services in UK [30]. Nevertheless, the economic benefits such as reduced hospitalization and mortality should be investigated among the Chinese patients.

Our cost-minimization analysis using a simple illustration for a treatment period of slightly over 5 years shows an estimated total cost savings of RMB 38,000 for a patient treated with sevelamer instead of lanthanum. However, the uncertainty in this analysis lies within the variability of dose-relativity ratio between sevelamer and lanthanum. Based on the current retail prices of Renvela® and Fosenol® in China, the inflection point is slightly below 2.65, at which where there is no daily cost difference between the two non-calcium phosphate binders. In other words, the cost of a daily dose of 5,464 mg of sevelamer would be equivalent to that of a daily dose of 2,062 mg of lanthanum. This is far above the mean dose-relativity ratio of 2.13 as shown in the clinical study by Sprague et al. and 2.27 in the recent study using real world observational data in US by Keith et al. [24]. On a separate note, a dose relativity ratio of 2.08 for sevelamer: lanthanum could be derived based on the relative phosphate binding coefficients estimated for sevelamer (0.75), lanthanum (2.0), calcium carbonate (1.0) and calcium acetate (1.4) in a review by Daugirdas et al. in dialysis patients [36]. In addition, a local double blind, placebo controlled and randomized clinical study of 205 dialysis patients with hyperphosphatemia reported an average sevelamer dose of 4.5 g [37] within the range of above estimated sevelamer daily doses from two different dose-relativity ratios. In reference to this average daily dose of sevelamer, the dose relativity ratio for sevelamer dose subgroup 2,400 to 4,800 mg daily was 2.1 in Wilson et al. similar to the ratio of 2.13 (6,400 mg/3,000 mg) reported by Sprague et al. [21]. In fact, a lower ratio of 1.45 was estimated for the same sevelamer dose subgroup in Keith et al. [24]. Therefore, we believe that our analysis has been conservative in concluding the potential saving of patients treated with sevelamer in the context of China.

However, we recommend that a clinical study on dosing conversion between sevelamer and lanthanum to be conducted among the Chinese patients as the dose-relativity ratio may vary by race. Furthermore, serum phosphate level and hence the dose

Table 1 Cost analysis on sevelamer versus lanthanum.

	Scenario 1	Scenario 2
Equivalent Dose Relativity Ratio	2.13	2.27
Derived Daily Dose of Sevelamer	4,392 mg	4,681 mg
Daily Dose of Lanthanum	2,062 mg	2,062 mg
Daily Cost of Sevelamer (Renvela® 800 mg @ RMB 14.53)	RMB 79.77	RMB 85.01
Daily Cost of Lanthanum (Fosenol® 500 mg @ RMB 24.00)	RMB 98.98	RMB 98.98
Estimated Daily Cost Difference (sevelamer vs. lanthanum)	RMB - 19.21	RMB - 13.97
Estimated Annual Cost Difference (sevelamer vs. lanthanum)	RMB - 7,012	RMB - 5,099
Estimated Total Cost Difference – Average Life Years of 5.38 (sevelamer vs. lanthanum)	RMB - 37,725	RMB - 27,437
Estimated Total Cost Difference – Average Life Years of 4.33 (sevelamer vs. lanthanum)	RMB - 30,360	RMB - 22,079

of the binders are subject to dietary intakes which tend to be different due to race, culture and geographical region.

Conclusion

For the treatment of hyperphosphatemia in ESRD patients in China, our analysis demonstrate sevelamer being likely a cost-saving option compared to lanthanum, both non-calcium based phosphate binders that provide more efficacious alternatives than calcium-based phosphate binders.

Declaration of Funding

This study has been funded by Sanofi China, however; publication of the study results was not contingent upon sponsor's approval.

Conflicts of Interest

All authors declared no conflicts of interest.

References

1 Kong X, Zhang L, Zhang L, Chen N, Gu Y, et al. (2012) Mineral and bone disorder in Chinese dialysis patients: a multicenter study. BMC Nephrol 21: 13-116

2 Cronin R (2007) Treatment of hyperphosphatemia in chronic renal failure.

3 Chinese society of nephrology (2014) Guidance for diagnosis and treatment for CKD-MBD. Chinese Journal of Nephrology.

4 Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL (2005) Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol 16: 520-528.

5 Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, et al. (2008) Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 52: 519-530.

6 Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, et al. (2006) Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. Kidney Int 70: 351-357.

7 Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, et al. (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15: 2208-2218.

8 Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK (2001) 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 12: 2131-2138.

9 National Kidney Foundation (2003) K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 42: S1-S201.

10 Bommer J, Ketteler M, Ritz E (2012) Impact of oral calcium on mortality of dialysis patients--an underestimated risk? Nephrol Dial Transplant 27: 2628-2633.

11 Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, et al. (2000) Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 342: 1478-1483.

12 Budoff MJ, Kessler P, Gao YL, Qunibi W, Moustafa M, et al. (2008) The interscan variation of CT coronary artery calcification score: analysis of the Calcium Acetate Renagel Comparison (CARE)-2 study. Acad Radiol 15: 58-61.

13 Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, et al. (2008) Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med 358: 1336-1345.

14 Kidney Disease (2009) Improving Global Outcomes (KDIGO) CKD-MBD Work Group, KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl 113: S1-130.

15 Suki WN (2008) Dialysis Clinical Outcomes Revisited Investigators, Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients: results of a randomized clinical trial. J Ren Nutr 18: 91-98.

16 Jamal SA, Vandermeer B, Raggi P, Mendelssohn DC, Chatterley T, et al. (2013) Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet 382: 1268-1277.

17 Park H, Rascati KL, Keith MS, Hodgkins P, Smyth M, et al. (2011) Cost-effectiveness of lanthanum carbonate versus sevelamer hydrochloride for the treatment of hyperphosphatemia in patients with end-stage renal disease: a US payer perspective. Value Health 14: 1002-1009.

18 Vegter S, Tolley K, Keith MS, Lok CE, Soroka SD, et al. (2012) Cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in dialysis patients: a Canadian payer perspective. Clin Ther 34: 1531-1543.

19 Keith MS, Wilson RJ, Preston P, Copley JB (2014) Cost-minimization analysis of lanthanum carbonate versus sevelamer hydrochloride in US patients with end-stage renal disease. Clin Ther 36: 1276-1286.

20 Kasai S, Sato K, Murata Y, Kinoshita Y (2012) Randomized crossover study of the efficacy and safety of sevelamer hydrochloride and lanthanum carbonate in Japanese patients undergoing hemodialysis. Ther Apher Dial 16: 341-349.

21 Sprague SM, Ross EA, Nath SD, Zhang P, Pratt RD, et al. (2009) Lanthanum carbonate vs. sevelamer hydrochloride for the reduction of serum phosphorus in hemodialysis patients: a crossover study. Clin Nephrol 72: 252-258.

22 Chen N, Wu X, Ding X, Mei C, Fu P, et al. (2014) Sevelamer carbonate lowers serum phosphorus effectively in haemodialysis patients: a randomized, double-blind, placebo-controlled, dose-titration study. Nephrol Dial Transplant 29: 152-160.

23 Xu J, Zhang YX, Yu XQ, Liu ZH, Wang LN, et al. (2013) Lanthanum carbonate for the treatment of hyperphosphatemia in CKD 5D: multicenter, double blind, randomized, controlled trial in mainland China. BMC Nephrol 4: 14:29.

24 Keith MS, Sibbel S, Copley JB, Wilson RJ, Brunelli SM (2014) Real-World Dose-Relativity, Tablet Burden, and Cost Comparison of Conversion Between Sevelamer Hydrochloride/Carbonate and Lanthanum Carbonate Monotherapies. Clin Ther 36: 1431-1442.

25 Wilson RJ, Keith MS, Preston P, Copley JB (2013) The real-world dose-relativity of sevelamer hydrochloride and lanthanum carbonate monotherapy in patients with end-stage renal disease. Adv Ther 30: 1100-1110.

26 Kasai S, Sato K, Murata Y, Kinoshita Y (2012) Randomized crossover study of the efficacy and safety of sevelamer hydrochloride and lanthanum carbonate in Japanese patients undergoing hemodialysis. Ther Apher Dial 16: 341-349.

27 Shanghai Pharmaceutical Trade Association (2014) Shanghai Price information.

28 Bernard L, Mendelssohn D, Dunn E, Hutchison C, Grima DT (2013) A modeled economic evaluation of sevelamer for treatment of hyperphosphatemia associated with chronic kidney disease among patients on dialysis in the United Kingdom. J Med Econ 16: 1-9.

29 Brennan A, Akehurst R, Davis S, Sakai H, Abbott V (2007) The cost-effectiveness of lanthanum carbonate in the treatment of hyperphosphatemia in patients with end-stage renal disease. Value Health 10: 32-41.

30 Chen Y, Schweitzer SO (2008) Issues in drug pricing, reimbursement, and access in China with references to other Asia-Pacific region. Value Health 11: S124-129.

31 Bardel A, Wallander MA, Svardsudd K (2007) Factors associated with adherence to drug therapy: a population-based study. Eur J Clin Pharmacol 63: 307-314.

32 Taylor MJ, Elgazzar HA, Chaplin S, Goldsmith D, Molony DA (2008) An

economic evaluation of sevelamer in patients new to dialysis. Curr Med Res Opin 24: 601-608.

33 Manns B, Klarenbach S, Lee H, Culleton B, Shrive F, et al. (2007) Economic evaluation of sevelamer in patients with end-stage renal disease. Nephrol Dial Transplant 22: 2867-2878.

34 Huybrechts KF, Caro JJ, Wilson DA, O'Brien JA (2005) Health and economic consequences of sevelamer use for hyperphosphatemia in patients on hemodialysis. Value Health 8: 549-561.

35 Huybrechts KF, Caro JJ, O'Brien JA (2009) Prevention and management of hyperphosphatemia with sevelamer in Canada: health and economic consequences.Value Health 12: 16-19.

36 Daugirdas JT, Finn WF, Emmett M, Chertow GM (2011) Frequent Hemodialysis Network Trial Group. The phosphate binder equivalent dose. Semin Dial 24: 41-49.

37 Renvela® (2013) package insert. Sanofi China., Shanghai, China.