Cost-effectiveness analysis of paricalcitol *versus* calcitriol for the treatment of SHPT in dialytic patients from the SUS perspective

Análise de custo-efetividade de paricalcitol *versus* calcitriol no tratamento do HPTS em pacientes do SUS dialíticos, da perspectiva

Authors

Fabiana Gatti de Menezes [1,2,3]

Rodrigo Martins Abreu [1]

Alexander Itria [1]

[1] Universidade de São Paulo.
[2] Universidade Estadual de Campinas.
[3] AbbVie.

Submitted on: 12/11/2015.
Approved on: 01/20/2016.

Correspondence to:
Fabiana Gatti de Menezes.
AbbVie Farmacêutica LTDA.
Avenida Jornalista Roberto Marinho, nº 85, 7º Andar, Brooklin, São Paulo, SP, Brazil.
CEP: 04576-010
E-mail: fabiana.menezes@abbvie.com
AbbVie Farmacêutica LTDA, São Paulo, Brazil.

DOI: 10.5935/0101-2800.20160048

Abstract

Introduction: Secondary hyperparathyroidism (SHPT) is a consequence of chronic kidney disease. The treatment at the Brazilian Unified Heath System (SUS) is performed with calcitriol, a drug which favors hypercalcemia and/or hyperphosphatemia, hindering the control of SHPT. Another option is paricalcitol, which causes parathormone (PTH) suppression faster than calcitriol, with minor changes in calcium-phosphorus product and calcium and phosphorus serum levels. **Objective:** This study aims to develop a cost-effectiveness analysis of paricalcitol *versus* calcitriol for patients in dialytic treatment with SHPT, from the SUS perspective. **Methods:** A Markov decision model was developed for patients ≥ 50 years old with end stage renal disease in dialytic treatment and SHPT. Quarterly cycles and a lifetime time horizon were considered. Life years (LY) gained were assessed as clinical outcome. Clinical and economic inputs were obtained from systematic literature review and official databases. Costs are presented in Brazilian real (BRL), for the year 2014. **Results:** In the base case: paricalcitol generated a clinical benefit of 16.28 LY gained *versus* 14.11 LY gained with calcitriol, total costs of BRL 131,064 and BRL 114,262, respectively, determining an incremental cost-effectiveness ratio of BRL 7,740 per LY gained. The data robustness was confirmed by the sensitivity analysis. **Conclusions:** According to cost-effectiveness threshold recommended by the World Health Organization for 2013, the treatment of SHPT in patients on dialysis with paricalcitol is cost-effective when compared to calcitriol, from the public healthcare system perspective, in Brazil.

Keywords: cost-effectiveness evaluation; hyperparathyroidism, secondary; renal insufficiency, chronic.

Resumo

Introdução: O hiperparatireoidismo secundário (HPTS) é uma consequência da doença renal crônica. O tratamento no SUS é realizado com calcitriol, que favorece a hipercalcemia e/ou hiperfosfatemia, dificultando o controle do HPTS. Uma opção clinicamente relevante é o paricalcitol, que ocasiona a supressão do paratormônio (PTH) de forma mais rápida que o calcitriol e com menores alterações nas taxas séricas de cálcio, fósforo e do produto cálcio-fósforo. **Objetivo:** Este trabalho tem como objetivo desenvolver uma análise de custo-efetividade de paricalcitol *versus* calcitriol para pacientes em diálise com HPTS, perspectiva do SUS. **Métodos:** Foi desenvolvido um modelo de decisão de Markov para a população ≥ 50 anos, com DRC em diálise e HPTS. Foram considerados ciclos trimestrais e um horizonte temporal *lifetime*. O desfecho clínico avaliado foram os anos de vida ganhos. Dados foram obtidos a partir de revisão sistemática da literatura e bases de dados oficiais. Custos em reais (R$), ano de 2014. **Resultados:** No caso base: paricalcitol gerou benefício clínico de 16,28 anos de vida ganhos *versus* 14,11 anos de vida ganhos com calcitriol, custos totais de R$ 131.064 e R$ 114.262, respectivamente. A razão de custo-efetividade incremental de R$ 7.740 por ano de vida salvo. Dados robustos confirmados pela análise de sensibilidade. **Conclusão:** De acordo com o limiar de custo-efetividade recomendado pela Organização Mundial de Saúde para o ano de 2013, o tratamento de pacientes com HPTS em diálise com paricalcitol é custo-efetivo, comparado ao calcitriol, perspectiva SUS.

Palavras-chave: avaliação de custo-efetividade; hiperparatireoidismo secundário; insuficiência renal crônica.

Introduction

Secondary hyperparathyroidism (SHPT) is characterized by the increased serum level of parathormone (PTH) and is frequently related to chronic kidney disease (CKD). CKD is currently considered a serious world public health problem. It starts as a kidney injury that evolves into the slow and progressive loss of this organ function, causing, in its end stage (glomerular filtration rate below 15 ml/min), the need for artificial blood clearance methods (hemodialysis or peritoneal dialysis).[1,2]

According to the *Sociedade Brasileira de Nefrologia* [Brazilian Society of Nephrology] (SBN)[3] survey, in 2012, 97,586 patients were on dialysis in Brazil, with 84% of these patients performing the procedure in the *Sistema Único de Saúde* [Brazilian Unified Heath System] ("*SUS*"). Sesso *et al*. published a study analyzing 200 patients with end stage renal disease, on chronic hemodialysis, and showed that the mean global cost, per patient-year for this therapy was US$ 7,980 and US$ 13,428, under *SUS* and the Supplementary Health System perspectives, respectively. In Brazilian real, the mean cost was BRL 19,499.93 and BRL 32,812.66, respectively (exchange rate of November 2014, US$ 1=BRL 2.4436).[4,5]

In CKD, there is a decrease in the renal production of calcitriol (1-alpha-25-dihydroxivitamin D3), hypocalcemia due to the decrease of tubular reabsorption and hyperphosphatemia due to the decrease of its renal clearance. These changes in metabolism are the main responsible for the development of SHPT, virtually present in all patients with end stage chronic kidney failure.[2,6]

The treatment goals are to decrease PTH levels and to normalize the calcium and phosphorus serum levels, and primarily involve the administration of activated vitamin D.[7] Currently, calcitriol is the standard of care employed by *SUS*; however, it is responsible for the subsequent hypercalcemia, hyperphosphatemia and increase in calcium x phosphorus (CaxP) product, making it difficult to manage SHPT.[8] These mineral disorders may lead to vascular and soft tissues calcifications, contributing for the cardiovascular morbidity and mortality (coronary disease, acute myocardial infarction, heart failure).[9-11]

New generations of vitamin D analogues have been developed in order to decrease PTH levels with minimized effects on calcium and phosphorus absorption. Sprague *et al.*[12] evaluated the efficacy and safety of paricalcitol, a selective activation of vitamin D receptor *versus* calcitriol, in a randomized, double-blind, Phase III study with 236 patients with SHPT and on hemodialysis; the patients on paricalcitol group had a faster decrease in PTH levels and remained more days with these appropriate levels.

Still, patients treated with paricalcitol had significantly less episodes of hypercalcemia and/or CaxP product increase compared to patients treated with calcitriol. The faster PTH suppression and the association with lower changes in calcium and phosphorus blood rates and CaxP product, potentially led to the prevention of their associated complications and, consequently, to the decrease of the morbidity and mortality related to SHPT, making the treatment with paricalcitol a clinically relevant option in the management of this clinical condition.[9-11]

Thus, the objective of this study is to perform a cost-effectiveness analysis of paricalcitol *versus* calcitriol for patients with SHPT on dialysis, under *SUS* perspective.

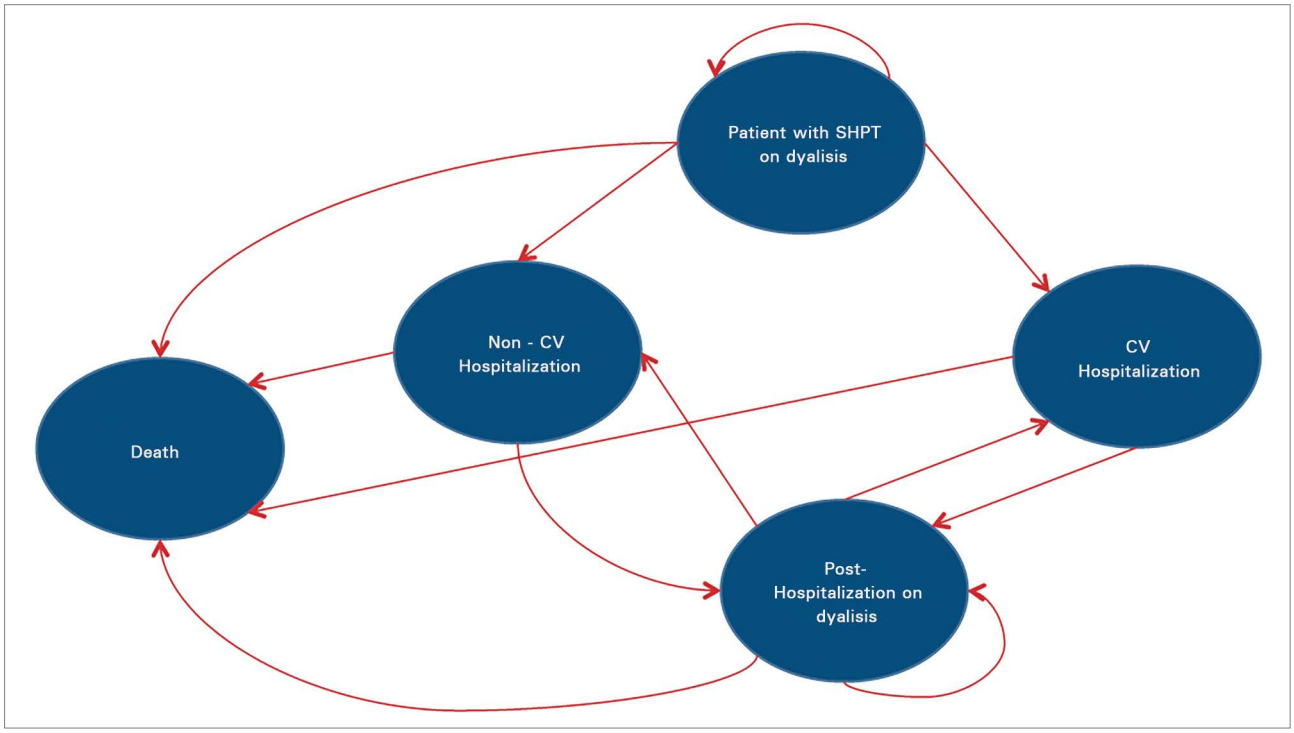
Methods

Decision model

A cost-effectiveness analysis was performed using a Markov model to simulate SHPT treatment with two different strategies: paricalcitol (5.0 mcg/mL) or calcitriol (1.0 mcg/mL). Adult subjects, both male and female, with CKD on dialysis and with SHPT were considered eligible to the treatment. The age of 50 years old was used for the entry in the model.

The following health states were included: patients on dialysis with SHPT, cardiovascular hospitalization, non-cardiovascular hospitalization, post-hospitalization and death. All the patients started as "dialysis with SHPT" status, where they could remain or migrate to "cardiovascular hospitalization", "non-cardiovascular hospitalization" and/or "death". After a hospitalization, the return to the initial status was no longer allowed, with migration to the "post-hospitalization" or "death" status (Fig. 1). Patients in "post-hospitalization" could remain in this status, be re-hospitalized and/or evolve to death. A lifetime time horizon and 3-month cycles were considered. Discount rates of 1.27% per trimester were applied to costs and clinical benefits.[13] Life years (LY) gained were considered as health outcome.

Figure 1. Decision model structure for patients with secondary hyperparathyroidism treated with paricalcitol or calcitriol.



Input data

Input data were searched in the literature in order to feed the model. The electronic searches were conducted until January 2014 in the databases MEDLINE via PubMed and LILACS using the following terms combined in a variety of strategies: paricalcitol, calcitriol, zemplar, and secondary hyperparathyroidism. Search engines included additionally Google® and other online tools. Electronic searches were supplemented by manual searches of bibliographic references. Information extracted from abstracts were not considered.

Dobrez *et al.*[14] showed a decrease in the risk of first hospitalization for cardiovascular and other causes, due to the use of paricalcitol (Table 1). In order to estimate the impact of paricalcitol in the reduction of hospitalizations, the decrease of relative risk and number of hospitalizations per year were considered. This way, patients on paricalcitol showed 2.4 hospitalizations per year, while those on calcitriol, 2.61 per year. A hospitalization rate for cardiovascular cause of 4.51% and 7.53% for other causes were considered.[4] Regarding mortality, the mean 3-month rate for patients on dialysis is 5.4%, and the 3-month mortality rate after a cardiovascular event is 19.98%. For patients on paricalcitol, a decrease of 16% was applied to the mortality rate.[15,16]

The model has four possible dose settings: calcitriol-paricalcitol dose ratio of 1:2, according to the daily dose defined by the World Health Organization (WHO);[17] calcitriol-paricalcitol dose ratio of 1:3; calcitriol-paricalcitol dose ratio of 1:4, both used in randomized clinical trials (RCT) published previously; [7,12] and the setting used by Sharma *et al.*[18] Also, there is the possibility to add the reduction ratio proposed by Sharma *et al.*[18] to the analysis, where after the first trimester, with a load dose, the patient remains in a maintenance dose 31% lower than the load dose.

Cost data

The model considered only the direct medical costs, under the perspective of the *SUS*. A BRL 36.82 and BRL 11.78 cost per vial was considered for paricalcitol and calcitriol, respectively (manufacturing price for paricalcitol without CAP (Price Adequacy Coefficient) and with 18% ICMS (Tax on Circulation of Goods and Services) and calcitriol with CAP and 0% ICMS - according to CMED (Drugs Market Regulation Chamber) and CONFAZ (National Council of Finance Policy).

Cardiovascular and non-cardiovascular hospitalization costs were included, calculated considering a hospitalization day cost (data obtained at Tabwin)

Table 1 Paricalcitol effect in decreasing the risk of first hospitalization

Paricalcitol effect	Rate
Decrease of risk of first hospitalization: all causes	13.70%*
Decrease of risk of first hospitalization: related to PTH	12.20%*
Infection	11.80%*
Cardiovascular (all)	12.10%*
Cardiovascular (without hypertension)	18.30%*
Non-infectious inflammation	11.80%†
Complication in the IV line site	10.50%‡
Other non-cardiovascular reasons	10.50%‡

PTH: parathormone; * $p < 0.0001$;† $p < 0.01$; ‡ $p < 0.05$.

multiplied by the mean time of hospitalization, in days, for calcitriol and paricalcitol.[4,14]

For the dialysis 3-month cost, the cost per dialysis obtained at SIGTAP (Table of Procedures Management System) and a total of 12 dialysis performed in a month were considered. Post-hospitalization was calculated through microcosting, with materials cost obtained at SIGTAP, and finally, for the calculation of death cost, Tabwin was used (data in 2011).

Sensitivity analysis

The univariate sensitivity analysis was performed with the following variables: paricalcitol cost, hazard ratio (12-month survival) and hospitalization cost. In the probabilistic sensitivity analysis, a distribution was attributed to any of the analyzed parameters. Gamma distribution was used for the number of hospitalizations per year and drug dose, for paricalcitol and calcitriol, as well as for the dialysis, hospitalization and paricalcitol costs. Beta distribution was used for dialytic patients mortality, reduction's percentage in the risk of mortality with the use of paricalcitol and risk of first hospitalization (for different causes).

Results

The calcitriol-paricalcitol dose ratio setting of 1:2 was considered as the base case, according to the daily dose defined by WHO.[17] The use of paricalcitol in this setting generated a clinical benefit of 16.28 LY gained *versus* 14.11 LY gained with the use of calcitriol, with total costs of BRL 131,064.58 and BRL 114,262.07, respectively, generating an incremental cost-effectiveness ratio (ICER) of BRL 7,740.31, per LY gained. Costs per patient, for each health status, are described on Table 2. Table 3 shows ICER (with discount rate in costs and benefits) in all possible model settings. It ranged from BRL 7,740.31 to BRL 17,683.21, according to the chosen setting.

The cost, per patient, with the acquisition of paricalcitol in a lifetime time horizon was BRL 21,583.85 in five years, *versus* BRL 17,956.86 for calcitriol. Additionally, medical direct costs included dialysis, with a cost of BRL 106,310.41 for paricalcitol and BRL 92,125.73 for calcitriol, and cardiovascular *versus* non-cardiovascular hospitalizations, with a cost of BRL 551.89 and BRL 773.46 for paricalcitol and BRL 948.06 and BRL 1,316.06 for calcitriol, respectively. Despite the cost of dialysis have been higher for the group treated with paricalcitol, this was due to lower mortality of these patients compared to calcitriol.

The following variables were evaluated in the univariate sensitivity analysis: cost reduction of paricalcitol, hazard ratio and hospitalization cost. The cost reduction of paricalcitol was the parameter with the higher impact on ICER per LY, as seen on Fig. 2. With a 35% discount in the cost of the drug, paricalcitol became dominant compared to calcitriol. A probabilistic sensitivity analysis with 1000 iterations was performed and it was seen that 100% of simulations showed results in quadrant 1, meaning that paricalcitol, compared to calcitriol, characterizes as a higher incremental effectiveness and cost in all the simulations, evidencing the model's robustness (Fig. 3).

Discussion

In this study, patients with chronic kidney disease and SHPT were evaluated with the objective of performing a cost-effectiveness analysis of paricalcitol *versus* calcitriol, under the *SUS* perspective. This way, a Markov decision model was developed, where patients were followed in a lifetime time horizon.

Table 2 Costs distribution, by health status per patient, in lifetime time horizon

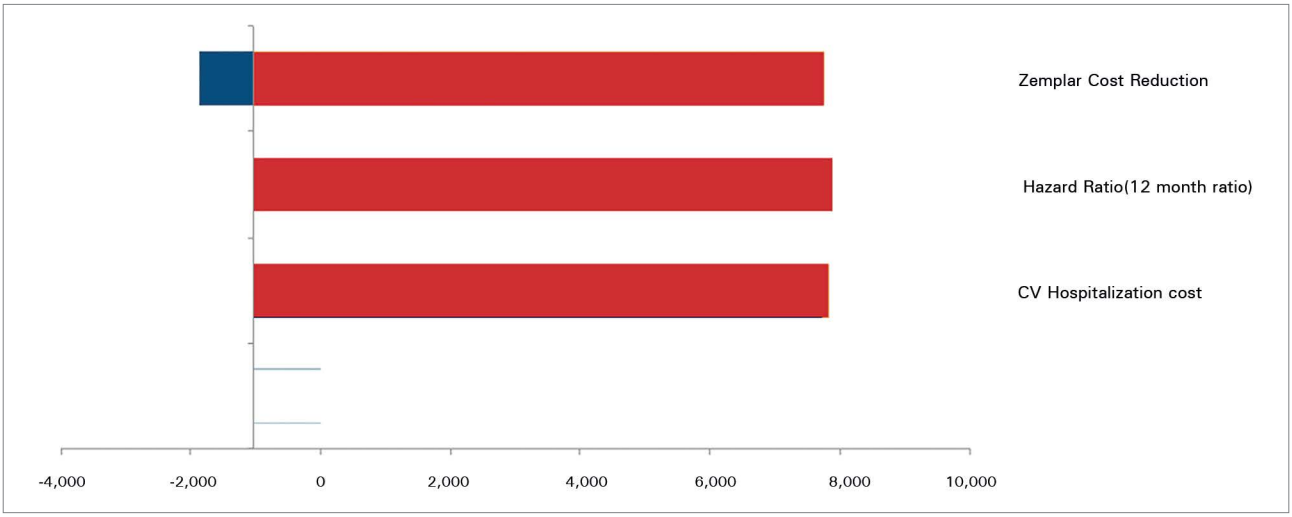
	Paricalcitol	Calcitriol	Incremental
CKD on dialysis	BRL 64,267.18	BRL 56,914.75	BRL 7,352.43
Overall hospitalization	BRL 14,016.38	BRL 13,835.05	BRL 181.32
Post-hospitalization	BRL 50,936.06	BRL 41,596.90	BRL 9,339.15
Death	BRL 1,844.97	BRL 1,915.36	-BRL 70.40
Total	BRL 131,064.58	BRL 114,262.07	BRL 16,802.51

CKD: chronic kidney disease.

Table 3 Incremental cost-effectiveness ratio (ICER) (paricalcitol *vs.* Calcitriol), according to the dose setting used

Setting	ICER (BRL per life year gained)
Dose 1:2 with dose decrease proposed by Sharma *et al.*[18] (2013)	BRL 7,740.31
Dose 1:2 without dose decrease proposed by Sharma *et al.*[18] (2013)	BRL 7,740.31
Dose 1:3 with dose decrease proposed by Sharma *et al.*[18] (2013)	BRL 8,358.74
Dose 1:3 without dose decrease proposed by Sharma *et al.*[18] (2013)	BRL 17,683.21
Dose 1:4 with dose decrease proposed by Sharma *et al.*[18] (2013)	BRL 17,683.21
Dose 1:4 without dose decrease proposed by Sharma *et al.*[18] (2013)	BRL 17,683.21
Dose proposed by Sharma *et al.*[18] (2013)	BRL 8,358.74

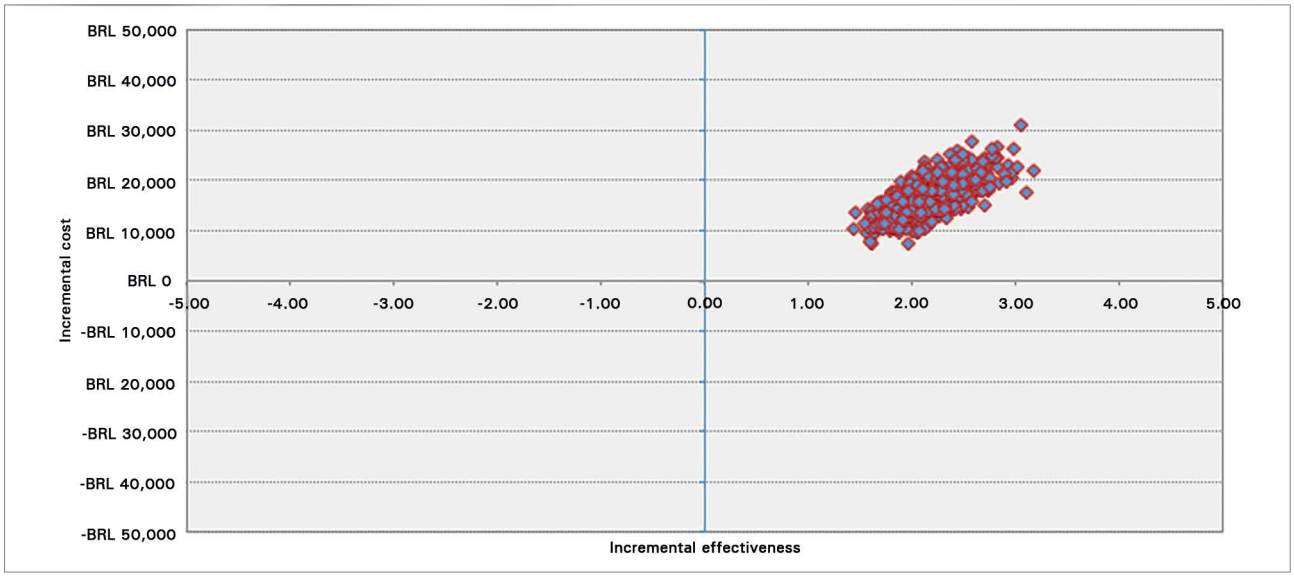
Figure 2. Tornado Diagram illustrating univariate sensitivity analysis of the effects of different parameters on the cost-effectiveness of paricalcitol *versus* calcitriol.



The analysis was made with a dose setting of 1:2, as it represents the Daily Defined Dose (DDD) for paricalcitol, defined by WHO.[17] The dose settings of 1:3 and 1:4 were used in randomized clinical trials.[7,12]. In the Sprague *et al.*[12] study, treatment with paricalcitol decreased PTH concentrations faster and with less sustained hypercalcemia episodes and increased Ca x P product than in the treatment with calcitriol. Ong *et al.*[7] found similar efficacy between the drugs. As these studies do not comprise maintenance doses and are far from the clinical practice, the DDD was used for the baseline case analysis.

Also, a 31% reduction was applied in the dose from month 6 on, as discussed by Sharma *et al.*[18] In this study, paricalcitol was administered orally or intravenously, three times a week. It was seen that the mean dose of paricalcitol decreased during the study period. The overall mean dose for the total study period was 6.0 mcg (SD=2.8), while the paricalcitol mean dose during the evaluation period (21–28 weeks) was 4.5 mcg (SD=3.7). Despite the decrease of the mean dose, there was a clinical improvement for patients on paricalcitol.

Figure 3. Probabilistic sensitivity analysis of the effects of different parameters on the cost-effectiveness of paricalcitol *versus* calcitriol.



The use of paricalcitol led to a clinical gain for the patients, with a decrease in the risk of first hospitalization for cardiovascular causes and other causes, according to Dobrez *et al*.[14] In this analysis, the use of paricalcitol implied in an incremental gain of 2.17 LY, when compared to calcitriol. In the United States, a cost-effectiveness analysis of paricalcitol *versus* calcitriol under the perspective of the outsourced multiple payer concluded that, in a 10-year time horizon, the use of paricalcitol leads to a 0.47 increase in gained years and 0.43 QALY, with an economy of US$ 1,941.[19]

Also, Teng *et al*.[15] has seen that the mortality rate was 16% lower (95% confidence interval, 10%-21%) among patients treated with paricalcitol than among patients treated with calcitriol. Thus, the costs related to dialysis and the acquisition of drugs are higher in patients on paricalcitol due to the increased number of live patients in this treatment arm.

According to WHO, the recommended cost-effectiveness threshold is of up to 3 times the Gross Domestic Product (GDP) per capita of the country where the analysis were performed per quality adjusted life year gained.[20] In Brazil, with the 2013 GDP per capita of BRL 24,065, the threshold is considered as BRL 72,195.[21] In this analysis, ICER was BRL 7,740.31 per LY gained.

Among the model limitations, the dosages used for calcitriol and paricalcitol and the price of the drugs must be highlighted. Paricalcitol cost had an important impact on ICER per LY. In spite of the limitations, the probabilistic sensitivity analysis has confirmed the model robustness.

Conclusions

The results presented in this study show that, in *SUS* perspective, the treatment of patients with SHPT on dialysis with paricalcitol is cost-effective, compared to calcitriol, with an ICER of BRL 7,740.31 per life year gained, according to the cost-effectiveness threshold recommended by WHO. Similarly, when other alternative dose settings are considered, paricalcitol remained cost-effective.

Acknowledgements

AbbVie Inc. funded the study. AbbVie was responsible for the study design, research, analysis, data collection, interpretation of data, and writing, reviewing, and approving of the publication. Rodrigo Martins and Alex Itria were responsible for the interpretation of data, writing and reviewing.

Disclosures

The design, study conduct, and financial support for the study were provided by AbbVie. AbbVie participated in the interpretation of data, review, and approval of the publication. Fabiana Gatti Menezes is an employee of AbbVie and own AbbVie stock.

References

1. Ferreira A. Diagnóstico clínico e laboratorial do hiperparatiroidismo secundário. J Bras Nefrol 2008;30:1-7.

2. Sociedade Brasileira de Nefrologia. Protocolo clínico e diretrizes terapêuticas para o tratamento do hiperparatireoidismo secundário em pacientes com doença renal crônica. São Paulo: Sociedade Brasileira de Nefrologia; 2013. 39 p. [cited 2016 Jul 11]. Available from: http://formsus.datasus.gov.br/novoimgarq/21112/3391420_109700.pdf
3. Sociedade Brasileira de Nefrologia. Censo de diálise - SBN 2012. São Paulo: Sociedade Brasileira de Nefrologia; 2012. 10 p. [cited 2016 Jul 11]. Available from: http://arquivos.sbn.org.br/pdf/publico2012.pdf
4. Sesso R, da Silva CB, Kowalski SC, Manfredi SR, Canziani ME, Draibe SA, et al. Dialysis care, cardiovascular disease, and costs in end-stage renal disease in Brazil. Int J Technol Assess Heal Care 2007;23:126-30. DOI: http://dx.doi.org/10.1017/S0266462307051665
5. Brasil. Banco Central do Brasil. Conversor de Moedas [Internet]. 2014. [cited 2014 Mar 14]. Available from: http://www4.bcb.gov.br/pec/conversao/conversao.asp
6. Brasil. Ministério da Saúde. Secretaria de Assistência à Saúde. Portaria SAS/MS n° 845, de 31 de outubro de 2002. Protocolo Clínico e Diretrizes Terapêuticas - Hiperfosfatemia na Insuficiência Renal Crônica: carbonato de cálcio, acetato de cálcio, hidróxido de alumínio, cloridrato de sevelamer. Brasília; 2002.
7. Ong LM, Narayanan P, Goh HK, Manocha AB, Ghazali A, Omar M, et al.; Oral Paricalcitol in ESRD Study Group. Randomized controlled trial to compare the efficacy and safety of oral paricalcitol with oral calcitriol in dialysis patients with secondary hyperparathyroidism. Nephrology (Carlton) 2013;18:194-200. DOI: http://dx.doi.org/10.1111/nep.12029
8. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Gestão e Incorporação de Tecnologias em Saúde. Paricalcitol para tratamento e prevenção do hiperparatireoidismo secundário. Brasília: Ministério da Saúde; 2013. 40 p.
9. Young EW, Albert JM, Satayathum S, Goodkin DA, Pisoni RL, Akiba T, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2005;67:1179-87. PMID: 15698460 DOI: http://dx.doi.org/10.1111/j.1523-1755.2005.00185.x
10. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000;342:1478-83. PMID: 10816185 DOI: http://dx.doi.org/10.1056/NEJM200005183422003
11. Ganesh S, Stack A, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001;12:2131-8.
12. Sprague SM, Llach F, Amdahl M, Taccetta C, Batlle D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. Kidney Int 2003;63:1483-90. PMID: 12631365 DOI: http://dx.doi.org/10.1046/j.1523-1755.2003.00878.x
13. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Ciência e Tecnologia. Diretrizes metodológicas: elaboração de pareceres técnico-científicos. 3 ed. Brasília: Ministério da Saúde; 2011. 80 p.
14. Dobrez DG, Mathes A, Amdahl M, Marx SE, Melnick JZ, Sprague SM. Paricalcitol-treated patients experience improved hospitalization outcomes compared with calcitriol-treated patients in real-world clinical settings. Nephrol Dial Transpl 2004;19:1174-81. DOI: http://dx.doi.org/10.1093/ndt/gfh123
15. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus M, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med 2003;349:446-56. PMID: 12890843 DOI: http://dx.doi.org/10.1056/NEJMoa022536
16. Sesso R de CC, Lopes AA, Thomé FS, Lugon JR, Burdmann EA. Censo brasileiro de diálise, 2009. J Bras Nefrol 2010;32:380-4. DOI:http://dx.doi.org/10.1590/S0101-28002010000400007
17. WHO Collaborating Centre for Drug Statistic Methodology. ATC/DDD [Internet]. 2013 [cited 2014 Mar 14]. Available from: http://www.whocc.no/atc_ddd_index/?code=H05BX02
18. Sharma A, Ketteler M, Marshall TS, Khan SS, Schumock GT. Comparative cost analysis of management of secondary hyperparathyroidism with paricalcitol or cinacalcet with low-dose vitamin D in hemodialysis patients. J Med Econ 2013;16:1129-36. PMID: 23834479 DOI:http://dx.doi.org/10.3111/13696998.2013.823092
19. Nuijten M, Andress DL, Marx SE, Sterz R. Chronic kidney disease Markov model comparing paricalcitol to calcitriol for secondary hyperparathyroidism: a US perspective. Curr Med Res Opin 2009;25:1221-34. DOI: http://dx.doi.org/10.1185/03007990902844097
20. Brasil. Ministério da Saúde. Secretaria-Executiva. Área de Economia da Saúde e Desenvolvimento. Avaliação econômica em saúde: desafios para gestão no Sistema Único de Saúde. Brasília: Ministério da Saúde; 2008. 104 p.
21. Brasil. Instituto Brasileiro de Geografia e Estatística (IBGE). Brasil em síntese. Contas nacionais, PIB - per capita [Internet]. 2012. [cited 2014 Mar 14]. Available from: http://brasilemsintese.ibge.gov.br/contas-nacionais/pib-per-capita