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Original Article

Cost-effectiveness analysis of cinacalcet versus vitamin D analogs in secondary hyperparathyroidism in end-stage renal disease patients on dialysis (Protocol)

Nilofar Sharahi[1], Majid Davari[2*], Tahereh Malakoutian[3], Zahra Gharibnaseri[4]

[1] *Department of Basic Science, School of Basic Science, Ahar Branch, Islamic Azad University, Ahar, Iran*
[2] *Department of Pharmacoeconomics and Pharmaceutical management, School of Pharmacy, Pharmaceutical Administrations and Pharmacoeconomics Research Center, Tehran University of Medical Sciences, Tehran, Iran*
[3] *Department of Nephrology, School of Medicine, Academy of Medical Sciences of Iran, Tehran, Iran*
[4] *Department of Pharmacoeconomics and Pharmaceutical Administration, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran*

ABSTRACT

Background: Chronic kidney disease (CKD) is an irreversible and progressive deterioration of renal function. The terminate stage of CKD is known as end-stage renal disease (ESRD) at which the patient needs a renal replacement therapy such as dialysis. Secondary hyperparathyroidism (SHPT) - excessive production of parathyroid hormone - is a common complication of impaired renal function. Patients with ESRD are likely at high risk for varying degrees of SHPT. Guidelines recommend pharmacotherapy as the main treatment of SHPT. Cinacalcet is a new medicine for treating patients with SHPT. The aim of this paper was to describe the background, rationale, objectives, design, and methodology of cost-effectiveness analysis of cinacalcet for SHPT in ESRD patients.

Methods: We will perform a systematic review of the approved databases and literature to collect randomized control trials on SHPT. The definitions, data sources, methods of data gathering, and data generating will be explained in this paper. One-way sensitivity analysis will be used for estimating the robustness of our results.

Conclusion: This study helps to obtain information concerning the cost-effectiveness of using cinacalcet in the treatment regimen of SHPT patients. The result will assist policy makers and physicians to support the most cost-effective pharmaceutical therapy for SHPT patients. This would increase allocative efficiency of the health-care delivery system in Iran.

Keywords: End-stage renal disease; Secondary hyperparathyroidism; Cinacalcet; Cost-effectiveness

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1. Introduction

Chronic kidney disease (CKD) is an irreversible and progressive deterioration of renal function [1]. The terminate stage of CKD is known as end-stage renal disease (ESRD) at which the patient needs a renal replacement therapy (RRT) such as dialysis. Secondary hyperparathyroidism (SHPT) - excessive production of parathyroid hormone (PTH) - is a common complication of impaired renal function [2]. Patients with ESRD are likely at high risk for varying degrees of SHPT. Hyperparathyroidism disrupts the body's biochemical balance resulting in a range of symptoms such as fractures, bone pain, and cardiovascular diseases. The pathogenesis of SHPT in CKD is complex and has not been fully understood. A range of factors has been implicated in the pathogenesis of SHPT including reduced serum calcium, increase in plasma phosphate level, decreased vitamin D activity, parathyroid tissue hyperplasia in response to uremia and altered parathyroid sensitivity to plasma calcium. The attainment of target level for serum PTH, calcium and phosphate concentrations has been supported by national and international guidelines.

The main approaches to the treatment of SHPT are:

- Reduction in serum phosphate by the use of phosphate binding agents and dietary restriction
- Reduction in PTH by supplementation of vitamin D.

Parathyroidectomy may be indicated in cases of uncontrolled SHPT, typically with nodular parathyroid hypertrophy and very high level of PTH [1].

First approved in the United States in 2004 as a calcimimetic agent, cinacalcet, and lowers elevated serum PTH level in dialysis patients [3]. Once hyperphosphatemia and hypocalcemia are adequately treated, PTH may be controlled within an acceptable target range (i.e., between 150 and 300 pg/mL); in such cases, no additional therapy is needed. However, if PTH level did not drop below 300 pg/mL, further therapy for hyperparathyroidism is indicated. Calcitriol (or a

*Corresponding author. Tel.: +98 21 64121137, Fax: +98 21 66482606, E-mail: m-davari@tums.ac.ir, Majid Davari
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synthetic vitamin D analog) or cinacalcet is the drug of choice, in such cases [4]. The first systematic review about the therapeutic role of cinacalcet in SHPT has been published in 2006 and showed that cinacalcet is more effective in bringing SHPT under control than standard care [1]. Li et al. [5] and Bellasi and Cozzolino [6] have confirmed Garside's findings indicating the superiority of cinacalcet over conventional therapy including parathyroidectomy. A recent review performed, in 2014, has provided evidence on the benefits and harms of cinacalcet therapy in certain patients, suggesting a reduction in need for parathyroidectomy in CKD and ESRD patients with elevated PTH level under cinacalcet therapy [7]. That said, nephrologists have started to prescribe cinacalcet to ESRD patients in Iranian health-care setting. However, the economic aspect of prescribing this medicine in this setting is not yet known, leading to an immediate need for a pharmacoeconomic study on different protocols recommending cinacalcet. The aim of this paper was to describe the background, rationale, objectives, design, and methodology of cost-effectiveness analysis of cinacalcet for SHPT in ESRD patients.

2. Methods

Overview

This study will be conducted in three stages for evaluating the effectiveness of cinacalcet in SHPT patients on dialysis. In the first stage, we will check all relevant data by conducting a systematic review on randomized clinical trials to find comparison results between cinacalcet and vitamin D efficacy. In the next step, the data on safety aspects of using cinacalcet will be examined. Finally, the cost of cinacalcet therapy will be obtained and compared with its alternative to perform a cost-effectiveness analysis.

Data Source

Effectiveness data source: We will use a systematic approach to extract efficacy data from confirmed databases and literature. Four databases including Cochrane library, PubMed, Scopus, and Google Scholar will be queried for randomized clinical trials. Literature searches will be carried out with no language or publication restrictions. Iranian search engines including IranDoc, IranMedex, and Scientific Information Database (SID) will also be checked. In addition gray literature will be covered in our search strategy including conference papers and theses obtained from Scopus and ProQuest databases, respectively. Finally, hand-searching will be performed both on journals which are identified with a high yield of trial reports and reports identified by published systematic reviews using backward citation searching.

Search strategy: A sensitive systematic search strategy will be utilized to cover all published data sources. To achieve the most comprehensive and efficient data, search terms used for the above-mentioned medical electronic databases will be extracted using the Medical Subject Headings of PubMed (and entry terms or synonyms), and Emtree. In addition, we will search IranMedex, SID, and IranDoc, which are among the most comprehensive national electronic databases, with the most coverage of Iranian public health and medical journals. All of these databases will be searched to find randomized control trials (RCTs) related to the objectives of our study, with no limitation in language and point. Table 1 shows our search strategy and search terms for ESRD patients with SHPT and related interventions in detail.

Table 1. Search strategy

Central	(#1 Therapeutics) (#2 Intervention studies) (#3 (therap* or intervention* or treat*)) (#4(#1 or #2 or #3) (#5 kidney failure chronic) (#6 ESRD) (#7 End stage renal disease) (#8 CKD) (#9 chronic kidney disease) (#10 #5 OR #6 OR #7 OR #8 OR #9) (#11 SHPT) (#12 secondary hyperparathyroidism) (#13 hyperparathyroidism secondary) (#14 #11 OR #12 OR #13) #15 (#4 AND #10 AND #14)
PubMed	(Sensipar OR AMG 073 OR KRN 1493 OR AMG073 OR cinacalcet hydrochloride OR "alpha methyl N (3-(3-(trifluoromethyl) phenyl) propyl)-1-naphthalenemethanamine, (alpha) hydrochloride" OR cinacalcet) AND ("End stage renal disease" OR ESRD OR "End stage kidney disease" OR (End-stage kidney AND Disease) OR (Kidney disease AND End-stage) OR "Chronic kidney failure" OR "End-stage renal disease" OR (Disease AND End-stage renal) OR (Renal disease AND End-stage) OR (Renal disease AND End stage) OR "End-stage renal failure" OR (Renal failure AND End stage) OR (Renal failure AND chronic))
Scopus	(Sensipar OR amg 073 OR krn 1493 OR amg073 OR cinacalcet hydrochloride OR "alpha methyl N (3-(3-(trifluoromethyl) phenyl) propyl)-1-naphthalenemethanamine, (alpha) hydrochloride" OR cinacalcet) AND ("End stage renal disease" OR ESRD OR "End stage kidney disease" OR (end-stage kidney AND disease) OR (kidney disease AND end-stage) OR "Chronic Kidney Failure" OR "End-stage renal disease" OR (disease AND end-stage renal) OR (renal disease AND end-stage) OR (renal disease AND end stage) OR "End-stage renal failure" OR (renal failure AND end stage) OR (renal failure AND chronic)) AND (EXCLUDE (DOCTYPE, "cp") OR EXCLUDE (DOCTYPE, "ch") OR EXCLUDE (DOCTYPE, "bk"))
Conference Paper	(ALL ((sensipar OR AMG 073 OR AMG073 OR cinacalcet hydrochloride OR cinacalcet)) AND ALL (("End stage renal disease" OR ESRD OR "End stage kidney disease" OR (end-stage kidney AND disease) OR (kidney disease AND end-stage) OR "Chronic kidney failure" OR "End-stage renal disease" OR (disease AND end-stage renal)))) AND (LIMIT-TO (DOCTYPE, "cp"))
Google Scholar	(Cinacalcet OR Sensipar OR AMG 073) AND ("End stage renal disease" OR ESRD OR "End stage kidney disease" OR "Chronic kidney failure" OR "End-stage renal disease" OR "End-Stage Renal Failure")
ProQuest	(Sensipar OR AMG 073 OR KRN 1493 OR AMG073 OR cinacalcet hydrochloride OR "alpha methyl N (3-(3-(trifluoromethyl) phenyl) propyl)-1-naphthalenemethanamine, (alpha) hydrochloride" OR cinacalcet) AND ("End stage renal disease" OR ESRD OR "End stage kidney disease" OR (End-stage kidney AND disease) OR (Kidney disease AND End-stage) OR "Chronic kidney failure" OR "End-stage renal disease" OR (Disease AND End-stage renal) OR (Renal disease AND End-stage) OR (Renal disease AND End stage) OR "End-stage renal failure" OR (Renal failure AND End stage) OR (Renal failure AND Chronic)) AND (Secondary hyperparathyroidism OR "Hyperparathyroidisms, secondary" OR Secondary hyperparathyroidisms)

Then, we will review and collect data from unpublished data sources such as conferences paper, and reference lists and adapt the strategy for them. A list of most related journals will be retrieved via Scopus and checked for relevant papers.

Inclusion criteria: Published papers and gray literature published without any language or publication restrictions will be included in the study. All papers that include data RCTs that studied therapeutic role of cinacalcet in patients with ESRD will be selected. We will be included ESRD patients (the fifth stage of CKD) with SHPT, and we will be considered all age groups without gender restriction. We will consider prescribing cinacalcet HCl (AMG-073, Sensipar®) including all doses and with all of the plans of therapy for decreasing level of PTH in ESRD patients with SHPT. We will consider vitamin D steroles as the comparator group. The decrease rate in PTH level, calcium, phosphate and Ca × P level, and the rate of parathyroidectomy will be considered as primary outcomes. Hospitalization (incidence of cardiovascular events and incidence of fractures) will be considered as secondary outcomes. ESRD patients with SHPT without dialysis, primary hyperparathyroidism will be excluded from the study. Non-RCTs including reviews and observational studies will be rejected.

Two experts will review the titles, abstracts, and finally the full-text of the articles and using a checklist; they will critically appraise the full-text of selected articles. If there is any disagreement, the reviewers will discuss the eligibility of the articles and will decide about it.

Study selection process: All title will be checked by two reviewers. Duplicated studies, pharmacokinetics, animal studies, case–control, and systematic reviews will be excluded. Disagreement between the two reviewers will result by a third reviewer to decide about including study. According to the inclusion criteria, random clinical trials, both in English and Persian published before April 2015 will be included.

Quality assessment: Two reviewers will work independently to assess risk of bias using criteria described in the "Cochrane Handbook for Systematic reviews of Interventions" [8]. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting. Each of the above items will obtain a score, and the total score will be calculated. Two reviewers will independently evaluate all selected articles via this method. In case of disagreement between the reviewers, consensus adjudication will be performed. A third reviewer will be controlled and confirm the decisions made by the two other reviewers.

Data extraction: After reviewing all selected articles, the needed information will be extracted and entered in the standard data extraction form. This sheet has information on aggregated data including mean, standard error of mean, characteristics of the study (design, methods of randomizations), participants, interventions, and outcomes (types of outcome measures, adverse events). Two independent reviewers will independently extract data. Any discrepancies will be resolved by discussion. Data will be extracted from finally selected full-text articles.

Cost data source: Cost data within our study include direct costs and are mainly focused on pharmaceutical costs. To obtain cost data, pharmaceutical sales data, and prices will be gathered from the Food and Drug Organization. In addition, community pharmacies will be checked for comparing price and sales data.

Statistical Methods and Analysis Plans

If relevant heterogeneity is detected (I^2 statistic > 50%) or the meta-analysis is inappropriate for any other reason, we will not combine the results but undertake a narrative analysis of the studies, providing a descriptive presentation of the results.

We will pool data if no relevant heterogeneity is detected, using a fixed effects model in case there are less than three trials and random effects model elsewhere.

The influence of the statistical model used to pool data in the effects being evaluated will be assessed through deterministic sensitivity analysis.

3. Discussion

The aim of this paper was to describe the background, rationale, objectives, design, methodology, and methodology of cost-effectiveness analysis of cinacalcet for SHPT in ESRD patients. Literature shows increase in the prevalence and incidence rate of ESRD [9]. The incidence rate of ESRD among African-Americans is disproportionately higher than whites from the United States (1000 vs. 275 in one million population per year, respectively) [10]. Between the years 1997 and 2007, 35 thousand Iranian patients have received RRT. Showing a 130% increase through the last 6 years [11].

In this study, we described the study protocol for evaluating the cost-effectiveness of cinacalcet for CKD patients that suffer from SHPT. Most of the ESRD patients fall in the described category. These patients have significantly lower health-related quality of life (QoL) than the general healthy population [1].

There is an inverse relationship between severity of CKD and QoL. In other words, higher grades of CKD are correlated with lower QoL and higher prevalence of QoL impairments [12]. Despite the evidence demonstrating that cinacalcet brings biochemical markers of SHPT to target levels more effectively than standard treatment, a combination of factors leads to cinacalcet appearing to represent relatively poor value for money [1]. Thus, we also decide to assess economic evaluation of cinacalcet to consider any necessary change in treating SHPT patients in Iranian setting. Leading policymakers and health insurers to make evidence based decisions in allocating resources for ESRD.

There are some limitations in our study: (a) our limited access to some of full-text articles is the main limitation of our study, hence, we will contact the authors to convince them for collaboration; (b) we do not have access to indirect medication cost and solutions therefore our study is restricted to direct medical cost. The database used in our study lacks data on indirect medication cost; (c) uncertainty of the results is another limitation, and we will try to reduce its impact through running sensitivity analysis.

4. Summary

By determining the effectiveness and cost-effectiveness of cinacalcet in Iran, we will know more about possible effective therapies for SHPT patients in the country. In addition,

evidence will be developed for treating these patients efficiently. This would increase allocative efficiency of the health-care delivery system in Iran.

5. Conflict of Interests

Authors have no conflict of interests.

6. Acknowledgments

None.

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