



# Economic Evaluation of Denosumab for Treatment of Postmenopausal Osteoporosis: A Systematic Review

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## Abstract

**Background:** We aimed to review the systematic economic evaluation of denosumab versus than alternative drugs and oral bisphosphonates of postmenopausal osteoporosis in women and help health system policy makers for prioritizing and optimally allocate limited health resources.

**Methods:** We examined the databases of PubMed, Web of Science, Embase, Scopus, Cochrane Library, ProQuest. Strategy search was designed based on keywords. Inclusion criteria were: studies that conducted economic evaluation denosumab compared to oral bisphosphonates for the treatment of osteoporosis in postmenopausal women. Cost-effectiveness studies conducted using decision analysis models based on the economic evaluation approach; studies with available full-text papers; and studies written in English and published between 2010 and 2020. After selecting articles based on inclusion and exclusion criteria, data were extracted and the results were summarized. The quality of the articles was evaluated using the CHEERS checklist.

**Results:** Among 214 initial studies, 8 studies met the inclusion criteria. Most studies focused on the cost-effectiveness of denosumab compared with oral bisphosphonates for the treatment of osteoporosis. The study agreed interval ranged from 3 months to 5 years. The costs investigated in the studies were direct medical costs. In most studies, the use of denosumab significantly prevented fractures.

**Conclusion:** Denosumab is generally more cost-effective than alternative drugs and oral bisphosphonates (alendronate, risedronate, strontium ranelate, ibandronate, and untreated).

**Keywords:** Cost benefit analysis; Denosumab; Osteoporosis; Postmenopausal; Systematic review

## Introduction

Osteoporosis is a skeletal disease characterized by a reduction in bone mass and microstructures and a decline in bone tissue that is associated with increased fragility and increased risk of frac-

ture. Osteoporosis is one of the main threats of aging, and its prevalence among people aged over 50 years is 30% in women and 15% in men. Osteoporosis is characterized by a decrease in bone



mineral content along with bone matrix, so that bone loss is reduced, but bone composition remains normal (1).

Osteoporosis is preventable and treatable, but since it is a latent disease, it is usually undetectable until the final stages (2). It is a complex disease that is influenced by several factors, some of which are uncontrollable, such as age, sex, race, family history, menopause, and some other factors such as weight, mobility, nutrition, and smoking (3). Bone ability to cope with a fracture is dependent on several factors including bone mass, bone shape, and intrinsic characteristics of bone (4). There are several recommendations for preventing osteoporosis; for instance, it is recommended to adopt a diet high in calcium and vitamin D and have a daily intake of calcium-rich foods, especially low-fat and pasteurized dairy products (5).

Since the population of most Asian countries is aging, the incidence of fractures due to osteoporosis is also increasing in these countries. More than 50% of hip fractures are projected to occur in Asian countries by 2050 (6). The average prevalence of osteoporosis in Iran in 2012 was 17% (7).

The prevalence of osteoporosis increases with aging that is due to decreased bone tissue. Due to the decline of ovarian function in women during the post-menopausal period, the loss of bone mass is accelerated, and as a result, most women have the indications for the diagnosis of osteoporosis at the age of 70-80 years (3).

Denosumab is a monoclonal antibody produced by recombinant DNA technology. Denosumab ion binds specifically to the kappa-B nuclear ligand activating receptor (RANKL) and inhibits bone resorption markers. It is used to treat osteoporosis as well as to prevent bone fractures in people with solid cancer metastasized to the bone (8).

Due to increased life expectancy and an increasing percentage of the elderly population in recent years, the incidence and prevalence of osteoporosis and related fractures have been increasing, and this disease has become one of the most common diseases. In addition, advances in medical

technology and the introduction of new and sometimes costly preventive and therapeutic methods have made the disease economically striking.

In the health care sector, cost-effectiveness analyzes and, more generally, economic evaluations are performed to be aware of resource allocation decisions (9). The general objective of economic evaluations is to assist decision-makers to maximize the health benefits from a particular budget and provides a rationale for selecting specific programs among other programs when policy-makers are unable to implement all existing interventions and programs due to budget constraints. This method plays an important role in planning, managing and evaluating health systems, from designing payment methods to providers to improving access of households to health care (10). According to the above and the importance of orthopedic diseases and the costs that this group of diseases imposes on society, as well as the need to improve the allocation efficiency of limited health system resources in the field of orthopedic economics. We aimed to review the systematic economic evaluation of denosumab versus than alternative drugs and oral bisphosphonates of postmenopausal osteoporosis in women and help health system policy makers for prioritizing and optimally allocate limited health resources.

## **Methods**

We reviewed the economic evaluation studies of denosumab in comparison with bisphosphonates for the treatment of osteoporosis in postmenopausal women. To find these studies, we examined the databases of PubMed, Web of Science, Embase, Scopus, Cochrane Library, ProQuest. Strategy search was designed based on keywords. Databases were explored using search keywords, synonyms, and their combination with OR and AND operators to increase search sensitivity. The search strategy for PubMed database was as follows:

((Analyses[tiab] AND “Cost-Benefit”[tiab]) OR (Analysis[tiab] AND “Cost-Benefit”[tiab]) OR “Cost-Benefit Analyses”[tiab] OR “Cost Benefit Analysis”[tiab] OR (Analyses[tiab] AND “Cost Benefit”[tiab]) OR (Analysis[tiab] AND “Cost Benefit”[tiab]) OR “Cost Benefit Analyses”[tiab] OR “Cost Effectiveness”[tiab] OR (Effectiveness[tiab] AND Cost[tiab]) OR “Cost-Benefit Data”[tiab] OR “Cost Benefit Data”[tiab] OR (Data[tiab] AND “Cost-Benefit”[tiab]) OR “Cost-Utility Analysis”[tiab] OR (Analyses[tiab] AND “Cost-Utility”[tiab]) OR (Analysis[tiab] AND “Cost-Utility”[tiab]) OR “Cost Utility Analysis”[tiab] OR “Cost-Utility Analyses”[tiab] OR “Economic Evaluation”[tiab] OR “Economic Evaluations”[tiab] OR (Evaluation[tiab] AND Economic[tiab]) OR (Evaluations[tiab] AND Economic[tiab]) OR “Marginal Analysis”[tiab] OR (Analyses[tiab] AND Marginal[tiab]) OR (Analysis[tiab] AND Marginal[tiab]) OR “Marginal Analyses”[tiab] OR “Cost Benefit”[tiab] OR “Costs and Benefits”[tiab] OR “Benefits and Costs”[tiab] OR “Cost-Effectiveness Analysis”[tiab] OR (Analysis[tiab] AND “Cost-Effectiveness”[tiab]) OR “Cost Effectiveness Analysis”[tiab] AND (denosumab[tiab] OR Xgeva[tiab] OR “AMG 162” OR Prolia[tiab]) AND (“Perimenopausal Bone Loss”[tiab] OR (“Bone Loss”[tiab] AND Postmenopausal[tiab]) OR (“Bone Losses”[tiab] AND Postmenopausal[tiab]) OR “Postmenopausal Bone Losses”[tiab] OR (Osteoporosis[tiab] AND “Post-Menopausal”[tiab]) OR (Osteoporoses[tiab] AND “Post-Menopausal”[tiab]) OR (Osteoporosis[tiab] AND “Post-Menopausal Osteoporoses”[tiab]) OR “Post-Menopausal Osteoporosis”[tiab] OR “Postmenopausal Osteoporosis”[tiab] OR (Osteoporoses[tiab] AND Postmenopausal[tiab]) OR “Postmenopausal Osteoporoses”[tiab] OR (“Bone Loss”[tiab] AND Perimenopausal[tiab]) OR (“Bone Losses”[tiab] AND Perimenopausal[tiab]) OR “Perimenopausal Bone Losses”[tiab] OR “Postmenopausal Bone Loss”[tiab])

### *Inclusion and Exclusion Criteria*

Inclusion criteria were studies that conducted economic evaluation denosumab compared to oral bisphosphonates for the treatment of osteoporosis in postmenopausal women. Cost-effectiveness studies conducted using decision analysis models based on the economic evaluation approach; studies with available full-text papers; and studies written in English and published between 2010 and 2020.

We excluded papers that did not meet the following criteria: studies with partial cost-effectiveness analysis (such as effectiveness assessment, cost assessment, quality-of-life assessment); studies with a low score in the CHEERS checklist; studies written in languages other than English; and all protocols, conference abstracts, and letters to the editor.

### *Quality Assessment of Methodology of the Studies*

The reporting quality of the identified studies was measured against the CHEERS checklist for assessing economic evaluations. This checklist contains five questions with 24 criteria that assess the quality of each economic evaluation study in terms of title and abstract, introduction and problem statement, methodology, results, and discussion and conclusion (11). A study was deemed to be of excellent reporting quality if it scored 80% or higher, 75– < 80% very good quality, 50– < 75% good quality, and studies scoring below 55% were classified as poor quality.

### *Data Analysis*

After searching various databases, all retrieved studies were imported into EndNote software, and duplicates were removed. The remaining articles were independently studied by two researchers in the field. The PRISMA principles (preferential reporting items for systematic review and meta-analysis) were followed to retrieve the final studies. In the first stage, the title and abstract of the studies were reviewed and the relevant articles were selected according to the inclusion and exclusion criteria. Next, if the full text of a selected study was available, it was care-

fully reviewed and the final studies selected. At each of these stages, if there was no disagreement between the two researchers, the studies were reviewed by a third researcher. For each study entering the final stage, a sheet in Excel software to extract the initial data, including author name (s), year of publication, country of origin, study population, cost-effectiveness, intervention, comparator, cost calculation basis, The basis of cost-effectiveness analysis and cost savings.

## Results

The initial results of searches in databases were 214 articles. Among them, 138 articles were included in the study after removing the repeats, reduced to 83 articles after reviewing the title. The abstracts of 83 articles were reviewed and 39 articles received the criteria for entering the next stage. The full text of 39 articles was reviewed, of which 31 studies were excluded from the study based on inclusion and exclusion criteria. Finally, 8 studies were selected for a more detailed review (Fig. 1). No new and relevant study was found at the reference review stage of the final articles.

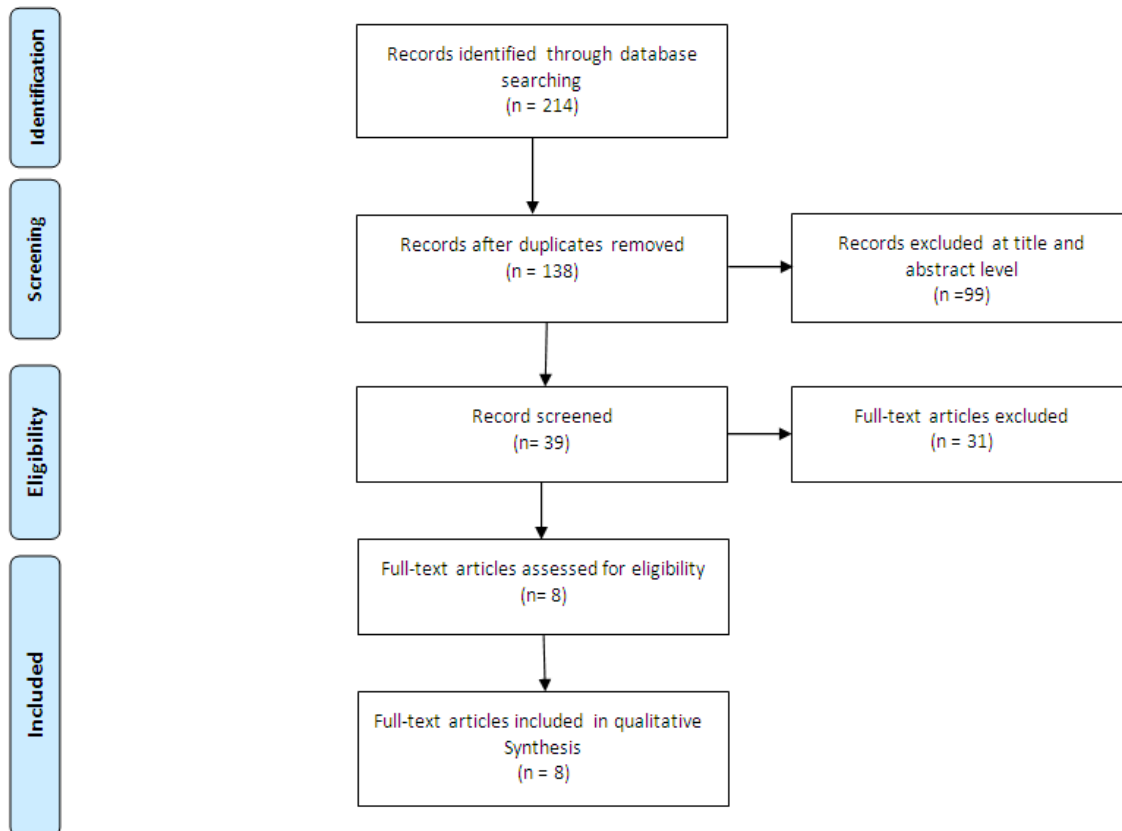


Fig. 1: Results of the systematic literature search

CHEERS checklist was used to evaluate the quality of these 9 studies. To avoid bias when evaluating the quality of articles, the researcher was unaware of the basic information of the article, such as the author's name, country, and year of publi-

cation. The results of the quality evaluation of the studies were acceptable and no study was excluded based on the quality criteria. The quality of the report of 8 studies was evaluated against 24 questions from CHEERS checklist, and for the cases

fully included in the study, a score of 1 with a mark of ✓ was assigned and for the cases not provided at all in the study, a score of 0 with a mark of ✗ was assigned. 8 articles with a score above 80% were recognized as "excellent quality" (Table 1).

After the quality evaluation, the data of the articles were extracted using the data form (Table 2).

The included studies include economic evaluations of the given intervention in several countries. Studies have been conducted in the United

States, Spain, Canada, Belgium, Sweden, Japan, and Thailand. Among the included studies, 3 studies from the perspective of the payer, (13,14,16) one joint study from the perspective of the government (15), the payer(18) and the society, 2 studies from the perspective of the society, 1 joint study from the perspective of the society(17) and the third-party payer (12) and 1 study from the perspective of the health system investigated the costs and advantages of the given intervention(8).

**Table 1:** Quality assessment of studies with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist

| Question / Author           | Title | abstract | Background | Population characteristic | Setting and location | Perspective | Comparators described | Time horizon | Discount rate | Outcomes and relevance | Measurement of effectiveness | Preference based outcomes | Estimating resources and | Currency, date | Model choice described | Assumptions | Analysis methods | Parameters of values | Incremental costs | sensitivity analyses | Heterogeneity explained | Findings and limitations | Funding source | Potential conflict of interest | Total | Percent satisfied |
|-----------------------------|-------|----------|------------|---------------------------|----------------------|-------------|-----------------------|--------------|---------------|------------------------|------------------------------|---------------------------|--------------------------|----------------|------------------------|-------------|------------------|----------------------|-------------------|----------------------|-------------------------|--------------------------|----------------|--------------------------------|-------|-------------------|
| Josep Darbà(12)             |       | ☐        | ☐          | ☐                         | ☐                    | ☐           | ☐                     | ☐            | ☐             | ☐                      | ☐                            | ☐                         | ☐                        | ☐              | ☐                      | ☐           | ☐                | ☐                    | ☐                 | ☐                    | ☐                       | ☐                        | ☐              | ☐                              | 20    | 83 %              |
| D. Chau(13)                 |       | ☐        | ☐          | ☐                         | ☐                    | ☐           | ☐                     | ☐            | ☐             | ☐                      | ☐                            | ☐                         | ☐                        | ☐              | ☐                      | ☐           | ☐                | ☐                    | ☐                 | ☐                    | ☐                       | ☐                        | ☐              | ☐                              | 23    | 95 %              |
| Mickae Hilgsmann(14)        |       | ☐        | ☐          | ☐                         | ☐                    | ☐           | ☐                     | ☐            | ☐             | ☐                      | ☐                            | ☐                         | ☐                        | ☐              | ☐                      | ☐           | ☐                | ☐                    | ☐                 | ☐                    | ☐                       | ☐                        | ☐              | ☐                              | 21    | 87 %              |
| B. Jönsson(8)               |       | ☐        | ☐          | ☐                         | ☐                    | ☐           | ☐                     | ☐            | ☐             | ☐                      | ☐                            | ☐                         | ☐                        | ☐              | ☐                      | ☐           | ☐                | ☐                    | ☐                 | ☐                    | ☐                       | ☐                        | ☐              | ☐                              | 23    | 95 %              |
| T. Mori(15)                 |       | ☐        | ☐          | ☐                         | ☐                    | ☐           | ☐                     | ☐            | ☐             | ☐                      | ☐                            | ☐                         | ☐                        | ☐              | ☐                      | ☐           | ☐                | ☐                    | ☐                 | ☐                    | ☐                       | ☐                        | ☐              | ☐                              | 19    | 80 %              |
| Anju Parthan(16)            |       | ☐        | ☐          | ☐                         | ☐                    | ☐           | ☐                     | ☐            | ☐             | ☐                      | ☐                            | ☐                         | ☐                        | ☐              | ☐                      | ☐           | ☐                | ☐                    | ☐                 | ☐                    | ☐                       | ☐                        | ☐              | ☐                              | 22    | 95 %              |
| Chatlert Pongchaiyaikul(17) |       | ☐        | ☐          | ☐                         | ☐                    | ☐           | ☐                     | ☐            | ☐             | ☐                      | ☐                            | ☐                         | ☐                        | ☐              | ☐                      | ☐           | ☐                | ☐                    | ☐                 | ☐                    | ☐                       | ☐                        | ☐              | ☐                              | 22    | 91 %              |
| Tomohiro Yoshizawa(18)      |       | ☐        | ☐          | ☐                         | ☐                    | ☐           | ☐                     | ☐            | ☐             | ☐                      | ☐                            | ☐                         | ☐                        | ☐              | ☐                      | ☐           | ☐                | ☐                    | ☐                 | ☐                    | ☐                       | ☐                        | ☐              | ☐                              | 22    | 91 %              |

**Table 2:** Summary characteristics and results of included studies

| <i>Author, Country</i>                    | <i>Year, Patient /Study Perspective</i>                                   | <i>Comparators/ Effectiveness measure</i>  | <i>Model / Time horizon</i>     | <i>Discount Rate/ Sensitivity analysis</i> | <i>Included cost</i>  | <i>ICER</i>   |
|---|---|--|---------------------------------|--|---|---|
| Josep Darbà et al., 2015, Spain(12)       | Spanish postmenopausal women/Spanish National Health System               | Alendronate, Risedronate, Ibandronate, Strontium ranelate/ QALYs                     | Markov model /6 months          | No, Yes                                    | Direct costs include: Annual drug costs, Non-drug costs Medical costs associated with hip fracture, Daily cost of nursing home/ long-term care, Cost of a physician visit, Cost of IV administration per injection. Cost of a nurse visit | The incremental cost-effectiveness ratios for denosumab versus no treatment, alendronate, risedronate, and ibandronate were estimated at €6,823, €16,294, €4,895, and €2,205 per QALY gained, respectively. denosumab dominated strontium ranelate.       |
| D. Chau et al, 2012, Canada(13)           | Women at high risk of fractures/ public payer                             | No therapy, alendronate, risedronate, or raloxifene /QALY                            | Markov model 6 month            | Yes 3% /Yes                                | Drug costs, Daily cost of long-term Care. Cost of a nurse visit   | Incremental cost-effectiveness ratios for denosumab vs. alendronate of \$60,266 (2010 CDN\$) (primary analysis) and \$27,287 per quality-adjusted life year gained.   |
| Mickael Hilgeman et al, 2011, Belgium(14) | Women (aged ≥60 years) for whom osteoporosis therapies/ .healthcare-payer | Alendronate and risedronate/ QALY  | Markov micro simulation/ 3 year | Yes 3%, Yes                                | Direct fracture cost, Monitoring cost.  | The cost effectiveness of denosumab compared with generic alendronate was estimated at €38 514, €22 and €27 862 per QALY for women aged 60, 70 and 80. The equivalent values were €37 167, €19 718 and €19 638 per QALY with prevalent vertebral fracture |
| B. Jönsson et al, 2011, Sweden,(8)        | Women aged 71 year/ societal perspective                                  | Generic alendronate, branded risedronate, strontium ranelate, and no treatment/ QALY | A markov cohort model/ 5 year   | Yes 3% /Yes                                | Daily cost of nursing home Cost of a BMD measurement Cost of a physician visit, Cost of a nurse visit, Drug costs   | Incremental cost-effectiveness ratios were estimated at €27,000, €12,000, €5,000, and €14,000, for denosumab compared with generic alendronate, risedronate, stronti-   |

|  |  |                                   |   |  |  |  |
|--|--|-----------------------------------|---|--|--|--|
| T. Mori,2017<br>japan(15)                          | Postmenopausal osteoporotic women/<br>societal<br>Healthcare sector and government.                                | oral alendronate/<br>QALY         | Markov micro simulation model/life time horizon | Formal healthcare sector, informal Healthcare sector, and non-healthcare sector costs and provided An impact inventory | Formal healthcare sector, informal Healthcare sector costs and provided An impact inventory  | um ranelate,<br>From a societal perspective, ICERs compared with alendronate of \$25,700/QALY at age 65 yr. denosumab was cost-saving compared with alendronate at ages 75 and 80 yr. From a healthcare sector or a governmental perspective, the ICERs were \$30,100 or \$26,800 at age 65 yr and \$6700/QALY or \$5800/QALY at age 70 yr, and denosumab remained cost-saving at ages 75 and 80 yr. Cost per QALY gained (\$US) for denosumab: \$US85,060 |
| Anju Parthan,2013<br>,US(16)                       | postmenopausal osteoporotic women/<br>third-party payer  | generic alendronate/<br>QALY      | Markov cohort model, life time horizon          | Yes 3%,<br>Yes   | Drug intervention, costs of treating fractures, drug administration and monitoring costs and long-term care costs  | The ICER for denosumab versus no pharmacologic treatment was 119,575 THB per QALY (3587USD per QALY) and the ICER for denosumab versus alendronate was 199,186 THB per QALY (5,976 USD per QALY).  |
| Chatlert Pongchaiyakulet al,2020,<br>Thailand,(17) | Postmenopausal women with femoral neck T-score $\leq$ -2.5, and history of vertebral fracture/societal perspective | No treatment and alendronate/QALY | Markov cohort model, life time horizon          | Yes 3%,<br>Yes   | Direct medical and non-medical care as well as the cost of informal care   | The ICER for denosumab versus alendronate was 199,186 THB per QALY (5,976 USD per QALY).   |
| Tomohiro Yoshizawa et al,2018<br>japan(18)         | 75-year-old Japanese women, societal perspective and third-party payers  | Oral alendronate/QALY             | Markov model/<br>5 yr                           | Yes 3%,<br>Yes   | Cost of alendronate, Cost of denosumab, Medical cost of hip fracture treatment, Medical cost of vertebral fracture treatment, Cost of nursing home (per year). | The ICER of denosumab versus alendronate treatment was estimated at US\$40,241/quality life year (QALY). The ICER of denosumab for 80-year-old women whose BMD was 60% of YAM was estimated at US\$22,469/QALY..   |

In all studies, the given intervention was denosumab, used to treat osteoporosis in postmenopausal women, and in most studies, it was compared with alendronate and risedronate. In economic evaluations, it is necessary to determine the time horizon both for the review and follow-up of the intervention itself and the consequences and costs related to it. Three studies were conducted over 6 months. 2 studies had an interval of 5 year, and one study had an interval of 3 years (4, 14, 18). 3 studies had no interval (15-17).

Among the final studies, one study was conducted on cost-effectiveness and other studies analyzed cost-effectiveness. Two studies showed no drop rate (12,15), and other studies considered drop rate.

In all studies, direct medical costs including costs of drug, nursing, diagnosis, and treatment were considered. Quality of life was calculated in all studies. Denosumab, prescribed for the treatment of osteoporosis during menopause, was more cost-effective than oral bisphosphonates. The cost per quality-adjusted life years (QALY) was determined in 7 studies. Only in a study, no cost per QALY was determined (8).

## **Discussion**

Osteoporosis has become a health problem around the world, especially in countries with a high average age population (19). According to periodic tests of vulnerability and osteoporosis evaluation in trial studies, a significant increase in bone mineral density, and reduction in the risk of hip and vertebral fractures, and generally the risk of osteoporosis in those receiving denosumab solution for injection have been reported (20,21). Today, not only it is important to pay attention to the medicinal value and clinical effectiveness of drugs but also more and more attention is paid to their economic aspects and cost-effectiveness compared to existing alternative and common drugs (22,23).

The present study was the first systematic review study that comprehensively investigates the re-

sults of economic evaluation studies of injected denosumab and compares it with other available drug interventions for the prevention and treatment of osteoporosis in postmenopausal women. In general, the present study showed that based on various economic decision-making criteria and clinical effectiveness used in various studies of health economic evaluation, the majority of studies have evidence of the cost-effectiveness of using denosumab compared with oral bisphosphonates (including alendronate and risedronate) in the prevention and treatment of menopausal osteoporosis.

Various economic evaluation studies have reported different cost-effectiveness measures for denosumab compared to alendronate. Thailand has the lowest incremental effectiveness cost of \$ 5,976 per QALY (17) and the US has the highest incremental effectiveness cost of \$ 85,060 (16).

A study on the cost-effectiveness of denosumab compared to other treatment options has shown that denosumab can be recommended as the first cost-effective treatment option compared to oral bisphosphonates (including alendronate) for the treatment of menopausal osteoporosis in women for ages over 60 years. The cost-effectiveness measure for this study was reported to be € 22,220 and € 27,862 for women aged 70 and 80 yr old, respectively, which, given the \$ 30,000 payment threshold for Belgium, compared to all other alternative drug interventions in these age groups denosumab is cost-effective (14).

On the other hand, injected denosumab is a cost-effective alternative to the treatment of osteoporosis in postmenopausal women, especially for women at high risk and those who do not adhere to the oral medication regimen. The cost-effectiveness of denosumab was compared with alendronate, risedronate, strontium ranelate, and the lack of treatment in Sweden, and the cost-effectiveness of denosumab was reported to be € 27,000, € 12,000, € 5,000, and € 14,000, respectively. The payment threshold of € 50,000 to € 60,000 per QALY has been reported in Sweden (8).



Patients' lack of complete adherence to medication regime is a major problem in the management of osteoporosis. Denosumab is a cost-effective solution to this problem compared to other available drug options such as alendronate and risedronate due to the annual dose with the injected regimen twice a year and no significant side effects. In this regard, according to the results of an economic evaluation study, the incremental cost-effectiveness measure for denosumab compared to alendronate is \$ 60,266 and the cost per QALY is \$ 27,287 in Canada. In this study, denosumab was introduced as the dominant treatment option (13).

Consistent with these results, in the United States, denosumab was more cost-effective in women over the age of 75 yr and at higher risk for osteoporosis than any other bisphosphonate treatment option which leads to economical cost savings. Therefore, by increasing age, and the risk of osteoporosis in postmenopausal women and various fractures, the cost of denosumab becomes more effective compared to other available drugs (16).

The cost-effectiveness of denosumab not only for treatment but also for the prevention of fractures and osteoporosis has been proven in various studies. For example, an economic evaluation study in Spain showed that denosumab compared to other available treatment options such as alendronate, risedronate, and ibandronate resulted in higher prevention and reduced risk of fractures in postmenopausal women, longer life-years gained, and more quality-adjusted life years. Denosumab has also been introduced as the dominant treatment option in this study as in previous studies (12).

In addition to the cost-effectiveness of denosumab in preventing or treating postmenopausal women at risk for fractures and osteoporosis, the efficacy and cost-effectiveness of this drug in treating osteoporosis among older women have been studied in two separate studies in Japan. In the first study, denosumab with a diet regimen every six months for 5 years compared to alendronate was introduced as the dominant and cost-effective treatment option for women aged

75 and 80 yr. The second study similarly and consistent with these results introduced denosumab compared to alendronate as a cost-effective drug among elderly women over 75 yr with a history of vertebral fractures and a bone density score of 65% (15,18).

Recently, another valuable study in the form of a cohort study investigated the cost-effectiveness of denosumab among women at risk for osteoporosis during menopause with a previous history of vertebral fractures in Thailand. Women at risk for using denosumab compared with no treatment showed fewer fractures, longer life years, higher quality-adjusted life years, and a significant reduction in the incidence of joint and vertebral fractures (17).

In this study, an attempt has been made to avoid any bias through a comprehensive and systematic search. However, excluded studies whose full text was not in English or could not be accessed could be a limitation. On the other hand, the lack of following a standard research method and the variety of models used in the final studies have made the continuity of their results difficult, which may have limited the possibility of analyzing the reported results from various dimensions. Moreover, the final studies entered a systematic review have reported the results of the economic evaluation for different years and investigated different cost items based on their study perspective, which in some cases may not be easy to compare and the generalization of results would be limited.

## **Conclusion**

Denosumab is predominantly cost-effective compared to existing alternatives and oral bisphosphonates (alendronate, risedronate, strontium ranelate, ibandronate, and untreated). Denosumab caused higher prevention of incidence of fractures and osteoporosis in women during menopause, life-years gained and quality-adjusted life years, especially in those over 75 yr of age, and in cases of poor adherence to oral medication regimens. Denosumab can also be the first-

line treatment option for the prevention and treatment of fractures and osteoporosis in women during menopause and old age.

## Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

## Conflict of interest

The authors declare that there is no conflict of interests.

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