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ORIGINAL PAPER

Denosumab versus bisphosphonates for the treatment of bone metastases from solid tumors: a systematic review

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Abstract

Background Bone metastases are highly prevalent in breast, prostate, lung and colon cancers. Their symptoms negatively affect quality of life and functionality and optimal management can mitigate these problems. There are two different targeted agents to treat them: bisphosphonates (pamidronate and zoledronic acid) and the monoclonal antibody denosumab. Estimates of cost-effectiveness are still mixed.

Objective To conduct a systematic review of economic studies that compares these two options.

Method Literature search comprised eight databases and keywords for bone metastases, bisphosphonates, denosumab, and economic studies were used. Data were extracted regarding their methodologic characteristics and cost-effectiveness analyses. All studies were evaluated regarding to its methodological quality.

Results A total of 263 unique studies were retrieved and six met inclusion criteria. All studies were based on clinical trials and other existing literature data, and they had high methodological quality. Most found unfavorable cost-effectiveness for denosumab compared with zoledronic acid, with adjusted ICERS that ranged from $4638–87,354 per SRE avoided and from US$57,274–4.81 M. per QALY gained, which varied widely according to type of tumor, time horizon, among others. Results were sensitive to drug costs, time to first skeletal-related event (SRE), time horizon, and utility.

Conclusions Denosumab had unfavorable cost-effectiveness compared with zoledronic acid in most of the included studies. New economic studies based on real-world data and longer time horizons comparing these therapeutic options are needed.

Keywords Neoplasms · Diphosphonates · Denosumab · Economics · Pharmaceutical · Cost-effectiveness analyses

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Introduction

Bone metastases are the most common type of metastasis for breast, prostate, colon, and lung cancer. Approximately, 65–75% of breast and prostate cancer patients and 15–40% of colorectal and lung cancer patients have evidence of bone metastases [1–3].

Bone metastases have different presentations and less frequently are silent. The most prevalent symptom of bone metastasis is pain (75%) [4], which is commonly severe and hard to manage. Osteolysis is thought to be responsible for bone pain, though exact mechanisms are undetermined [5].

Skeletal-related events (SREs) are common complications of bone metastases and occur in 46–68% of patients with bone metastases. SREs are related to pathologic fractures, spinal cord compression, need for bone radiation or bone surgery. Such conditions increase mortality rates and treatment costs [1–3].

These complications can significantly decrease quality of life, resulting in emotional distress and short- or long-term functionality decline [1–3]. Those can lead to productivity loss and work absenteeism on the onset of the event [6] and result in cost increase to the social security system. Thus, such events must be prevented.

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Currently, two classes of drugs are used for the treatment of bone metastases: bisphosphonates (e.g., clodronate, ibandronate, zoledronate, and pamidronate) and monoclonal antibodies (denosumab).

Bisphosphonates are the first target-specific drugs for bone tissue. They are deposited in sites of active bone remodeling, and the mechanism of action is related to the inhibition of osteolysis by the osteoclasts and induction of apoptosis of those cells [1, 7, 8].

Different generations of bisphosphonates are available, and some studies that compared the efficacy of different bisphosphonates showed that zoledronate is more efficacious compared with others [2, 3, 9]. However, other types of bisphosphonates have also been approved for use in bone metastases (e.g., pamidronate and ibandronate), although their use is limited by the type of bone lesion [10].

Bisphosphonates are administered through intravenous infusion and are usually well-tolerated. The most common adverse events (AEs) are fever, gastrointestinal symptoms, anemia, renal insufficiency, musculoskeletal pain, hydroelectrolytic imbalance, and, less commonly, osteonecrosis of the jaw [9, 11]. Zoledronic acid has been approved for the treatment of bone metastases from all types of solid tumors, osteoporosis, Paget's disease, and tumor-induced hypercalcemia [12]; the recommended dosage is 4 mg I.V. every 3–4 weeks, and the infusion time should not be less than 15 min [11].

Meanwhile, denosumab is a monoclonal antibody that inhibits the protein RANKL, which is essential for the differentiation, function, and survival of osteoclasts, thus inducing bone loss [13, 14]. It is generally well-tolerated by patients, and the most common AEs are fatigue, nausea, hypophosphatemia, and dyspnea. Less commonly, osteonecrosis of the jaw and hypocalcemia can occur [8, 14]. Recent studies have shown the efficacy and safety of denosumab for the treatment of bone metastasis [13].

In Europe and the United States, denosumab has been approved for use in the management of bone metastases from all solid tumors, multiple myeloma, and osteoporosis [12].

Treatments for bone metastasis are usually long and very costly. Technological and scientific advances often lead to the introduction of new treatment options that are increasingly sophisticated and expensive. However, limited financial resources can result in several barriers for introducing novel treatments in the market [15, 16].

In addition, the increasing interest and demand for new medical technologies oblige health professionals and decision makers to adopt more robust tools, particularly those deriving from economic analyses, as an aid for decision-making [17–19]. Although decision-making is a slow process, it is increasingly supported by systematic reviews and meta-analyses.

Different economic studies comparing denosumab with zoledronic acid have been conducted, and the results are mixed. Considering the high prevalence of bone metastasis, its impact on quality of life, and the economic influence it may have on the health system, determining the scope of available information on this issue and the best available evidence to make better informed decisions is important.

Aim

This study aimed to conduct a systematic review of economic studies that compare bisphosphonates with denosumab for the treatment of bone metastases from solid tumors.

Method

A systematic literature review of economic studies that compare the most used therapies for the treatment of bone metastasis was conducted.

We used the PICO strategy [20], in which the question "Is denosumab cost-effective compared with bisphosphonates (zoledronic acid and pamidronate) for the treatment of bone metastasis from solid tumors?" was used. **P**atients were those who had bone metastasis from solid tumors; **I**ntervention was denosumab; **C**omparison was bisphosphonates; **O**utcome was treatment incremental cost-effectiveness per SRE avoided.

This review was conducted following different steps. First, the Cochrane and Joanna Briggs Institute (JBI) databases were searched for existing systematic reviews on the subject. Second, keywords and synonyms related to bone metastases, bisphosphonates (pamidronate and zoledronic acid), denosumab, and economic studies were searched to compose the search strategy on each database. Third, these terms were combined through Boolean operators (AND/OR).

The following databases were searched in February 2017 and updated in July 2017: Cochrane, Embase, JBI, Lilacs, PubMed, Scopus, and Web of Science. After selection of the studies, their references were checked for any missing study that could contribute to the results of this review.

Studies were included if their sample comprised patients who had bone metastases from solid tumors, if the studies were complete economic studies of cost-effectiveness or cost utility, and if they compared denosumab with bisphosphonates. Studies were excluded if they included patient samples who had conditions other than bone metastases (e.g., menopause and multiple myeloma), if they did not present data on cost and effectiveness, if they did not directly compare the interventions of interest, or if the complete original

article was not available. The search was not limited by time, and only studies in English, Spanish, or Portuguese were included.

If any doubts regarding selection, inclusion, and assessment arise, a second reviewer would be consulted.

Results were presented in a flow diagram representing the search process among databases, adapted from the PRISMA statement [21]. Data were divided into categories for extraction and are presented in tables. One table included contextual characteristics of the studies, and the other presented economic data.

Economic data was used to evaluate the cost-effectiveness of denosumab compared to bisphosphonates by dividing the included studies into two groups, according to their outcome—SREs avoided or QALYs gained. All inputs were adjusted for the year of 2017, adjusted by 3% per year, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine [22]. Studies that presented costs in currencies other than US Dollars had those data exchanged considering currencies in July 1st, 2017.

All included articles were assessed using the JBI Critical Appraisal tool for Economic Evaluations [23] regarding its methodological quality. It is an 11-item scale in which the reviewer indicates the presence/absence or unclearness regarding relevant information that must be considered in an economic study.

Finally, studies were classified in levels of evidence based on the Oxford Centre for Evidence-Based Medicine—Levels of Evidence [24]. In this tool, one should consider the study design that generated evidence and specific methodological characteristics for different question types, including economics and decision-making.

Tables about the general characteristics of the study (i.e., country, journal, database etc.), the cost-effectiveness analysis and adjusted ICERs, methodological characteristics and methodological quality were provided.

Results

Search strategies retrieved 330 articles, with 67 being duplicates. Of the remaining 263 articles, 33 were selected by the title for abstract assessment, and 10 for full article review. Six studies were included in this article following the selection criteria.

Figure 1 shows the steps of the search process through a flow diagram.

Studies were excluded due to the following reasons: study methodology other than economic evaluations (reviews of literature, phase III trials, updates, and author correspondence), unavailability of the complete study (poster presentations in scientific events), did not include patients with bone metastases from solid tumors (multiple myeloma and osteoporosis), did not include treatment or comparison of interest, or the study addressed other issues, e.g., disease

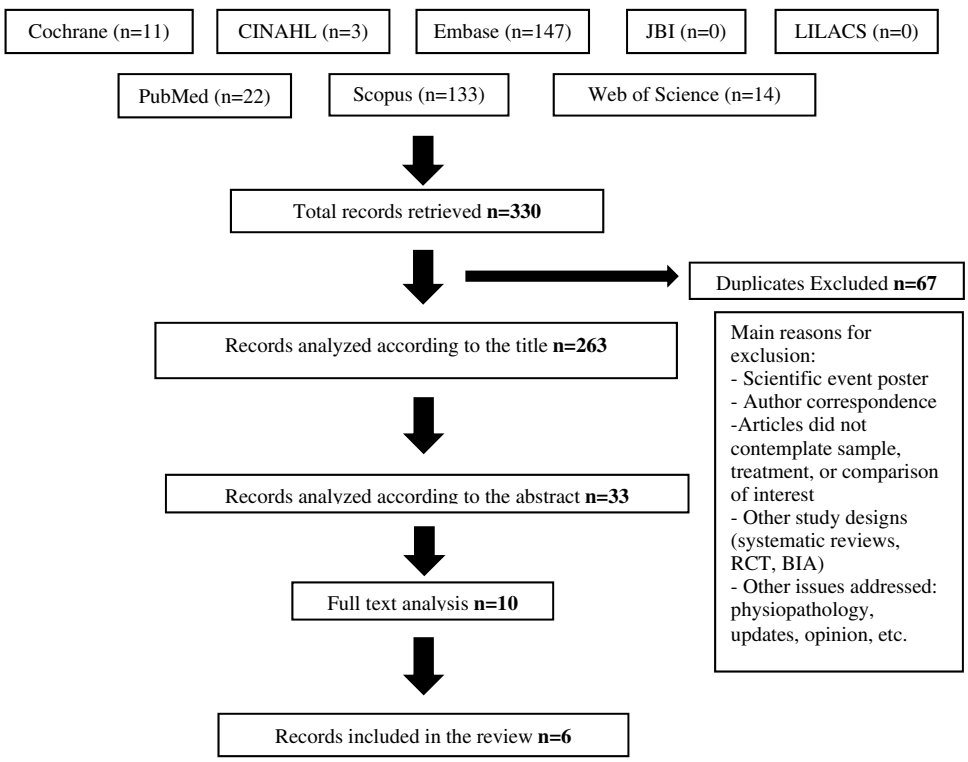

Fig. 1 Flow diagram of the search strategy for the systematic review (adapted from the PRISMA statement)

physiopathology, treatment updates, and symptom and disease management, among others.

Out of the 33 studies selected based on the abstract, 15 were poster presentations of economic studies in scientific events. Most of these posters were from the United States [25–31] (46.7%); three (20%) had an unclear origin, but were probably from the United States [32–34]; two were from Mexico [35, 36] (13.3%); and the other three were from Spain [37], the Netherlands [38], and Kazakhstan [39].

Five excluded studies were reviews of literature, from which one analyzed the methodological characteristics of the economic studies that evaluated denosumab compared with zoledronic acid [40]; one evaluated the pharmacoeconomics of bisphosphonates in metastatic bone disease but did not compare it with denosumab [10]; one was a health-economic review of zoledronic acid that included only prostate cancer patients [41]; one was an analysis of denosumab in men with castration-resistant prostate cancer that discussed its indications and some economic aspects of the disease [42]; and the remaining was a systematic review of literature of denosumab, which includes a cost-effectiveness analysis, but only included studies published before June 2011 [43]. Thus, this review did not include more recent studies and the potential impact of generic versions of zoledronic acid in their analyses.

Selected articles were in English and published from 2011 to 2013, and all of them were about cost-effectiveness or cost-utility analyses conducted in the United States (S1–S5) or Europe (S6), which shows the scarcity of this type of study in developing or undeveloped countries (Table 1). All included studies were funded by Novartis Pharmaceuticals (S1–S3, and S5) and Amgen Inc. (S4 and S6), developers of zoledronic acid and denosumab, respectively.

All studies were assessed in terms of its methodological quality, and most had a strong methodology and included the main information that economic studies must contain. Only one study and S6 had unclear data that could potentially affect the results, considering it did not present clear information about time adjustments for the analysis and, therefore, did not include all issues that could impact the results. Despite the good results from the methodological assessment, the generalizability of the analyses is unclear, considering all data were retrieved from the existing literature, even though all of them considered the uncertainties originated from the assumptions in the sensitivity analysis (Table 2).

None of the studies were developed from real-world implementation data. Authors used data from phase III trials and evidence from other existing literature that compared the use of zoledronic acid and denosumab for the treatment of bone metastases. All studies used Markov models to perform the economic evaluation from a third-party payer perspective (Table 3).

Moreover, the costs of the drugs, administration, and monitoring and treatment of SREs and AEs were considered in all studies. Outcomes were related to the avoidance of SREs and QALYs gained, according to data provided by phase III clinical trials (Table 4). Four studies considered the incremental costs of SREs avoided (S1 and S2) or QALYs gained (S3 and S5). Three studies presented estimates for both outcomes (S1, S4 and S6).

Despite being analyzed in three different years (2009–2011), in the studies conducted in the United States (S1–S5), the cost of denosumab was almost twice as high as zoledronic acid (Table 4). In three studies (S3, S5 and S6), the authors considered patent expiration of zoledronic acid and included the cost of generic ZA (50% of the price considered) in the sensitivity analysis.

Considering the analyses were performed in different years and costs vary according to inflation, costs and health effects were discounted by 3%, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine [22].

Table 5 shows 2017 adjusted ICERs found in all included studies. As expected, considering inflation rates over the years, ICERs were higher and still above the willingness-to-pay threshold considered in the studies. Only studies S4 and S6 presented their analyses categorized by type of cancer and found lower ICERs per SRE avoided. However, when considered QALYs gained, incremental costs achieve much higher values, which make denosumab not cost-effective relative to zoledronic acid.

Adjusted ICERs for 2017 were high and ranged from US$4638–87,354 per SRE avoided and from 57,274–4.8 M per QALY gained, and differed according to type of primary tumor (Table 5). The economic analyses showed zoledronic acid (83.3%) was cost-effective relative to denosumab. Results were sensitive to drug costs, time to first skeletal event, hazard and rates of SREs, utility values, and time horizons. Most studies found that, even when considered increased willingness-to-pay thresholds, denosumab is unlikely to be cost-effective (Table 4). Only one study out of six (S4) found denosumab to be cost-effective due to its high efficacy (ICER per SRE avoided: US$99,331–15,716; ICER per QALY gained: US$57,274–91,484), at WTP thresholds of US$100,000–200,000.

Based on the recommendations of the Oxford Centre for Evidence-Based Medicine (OCEBM), the level of evidence for S1–S5 is 1b, meaning that the study included sensitivity analysis and was based in sensible costs and alternatives. For this level of evidence, the grade of recommendation is A.

Still based on OCEBM, S6 has 3b level of evidence. Even though it comprised cost-effectiveness analysis and performed sensitivity analysis in different settings, data quality is dubious. The study estimated data that were not available for the context (e.g., denosumab prices), which could result

Table 1 General characteristics of studies included in the systematic review

Study	Authors	Title	Journal	Publication year	Language	Country	Database
S1	Xie et al. [44]	Economic evaluation of denosumab compared with zoledronic acid in hormone-refractory prostate cancer patients with bone metastases	J. Manag. Care Pharm	2011	English	United States	Cochrane Web of Science PubMed Embase
S2	Xie et al. [45]	Cost-effectiveness of denosumab compared with zoledronic acid in patients with breast cancer and bone metastases	Clinical Breast Cancer	2012	English	United States	Cochrane Web of Science PubMed Embase CINAHL
S3	Snedecor et al. [46]	Cost-effectiveness of denosumab versus zoledronic acid in the management of skeletal metastases secondary to breast cancer	Clin. Ther.	2012	English	United States	Cochrane Web of Science PubMed Embase CINAHL
S4	Stopeck et al. [47]	Cost-effectiveness of denosumab versus zoledronic acid for prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States	J. Med. Econ.	2012	English	United States	Cochrane PubMed Embase CINAHL
S5	Snedecor et al. [48]	Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a cost-effectiveness analysis	J. Med. Econ.	2013	English	United States	Cochrane PubMed Embase Scopus
S6	Yfantopoulos et al. [49]	The importance of economic evaluations in healthcare decision-making—a case of denosumab versus zoledronic acid from Greece. Third-party payer perspective	Forum Clin. Oncol.	2013	English	Greece	Embase Scopus

in potential bias. This level of evidence has grade of recommendation B.

Discussion

Economic studies are important during budgetary restriction period and global economic crisis because they can provide evidence for informed decision-making. Following that premise, assuming this type of studies should be developed worldwide is logical. It was not our intention to contrast cost-effectiveness publications around the world, but considering this type of literature is consumed by people in different countries, not only in the ones they are developed, it is important to draw attention to the context they were conducted, so consumers can know if the results can be transferred to their own settings.

Considering the findings in the present review, all analyses were conducted in the United States and European countries. Added to that, surprisingly, no studies conducted in Canada were retrieved. This country is known for requiring standardized analyses that follows Canada's national HTA

Table 2 Methodological assessment of studies included in the systematic review

Item	S1	S2	S3	S4	S6	S7
Defined question	Y	Y	Y	Y	Y	Y
Description of alternatives	Y	Y	N	Y	N	Y
Identification of costs and outcomes for each alternative	Y	Y	Y	Y	Y	Y
Accurate measurement of costs and outcomes	Y	Y	Y	Y	Y	Y
Credible valuation of costs and outcomes	Y	Y	Y	Y	Y	Y
Time adjustment for costs and outcomes	Y	NA	Y	Y	Y	U
Incremental analysis	Y	Y	Y	Y	Y	Y
Conduction of sensitivity analysis	Y	Y	Y	Y	Y	Y
Inclusion of all issues of concern	Y	Y	Y	Y	Y	U
Generalizability to the setting of interest	U	U	U	U	U	U

N no, *NA* not applicable, *U* unclear, *Y* yes

agency, the Canadian Coordinating Office of Health Technology Assessment (CADTH), to support decision-making about the purchase or coverage of a technology [50, 51]. One possible reason for this fact is that because Canada is a bilingual country (native language being French or English), meaning that if information regarding the drugs of interest were provided by a French-speaking province, those studies would have been excluded from our search strategy.

Noticeably, some presentations in scientific events were retrieved in the search, and some of them were conducted in developing countries, e.g., Mexico and Kazakhstan [34, 35, 38]. It could be due to the fact nations are in different stages in developing health technology assessments focused on economic reviews. Based on the results of the review, Canada, United States and European countries have progressed to determine methods to optimize their resources, whereas others are still beginning this process. For example, in Brazil, efforts to establish health technology assessments based on economic analyses for the decision-making process have been undertaken, beginning in the late 1990s. In 2011, CONITEC, a governmental agency responsible for the health technology assessments, was established and is still in development process [52, 53].

All studies retrieved used data from the existing literature, and built a Markov model based on phase III trials comparing the efficacy of denosumab relative to zoledronic acid for the treatment of metastatic bone disease. Consequently, all the results are based on clinical trial data, that is, following extremely controlled conditions. This means that the data may not always represent real life or the true response to the treatments in real-life conditions. Also, the results are subject to quality of the records and to the restrictions of the available data.

All authors of the economic analyses place the modeling technique as a limitation of their studies. This type of design and analysis are subject to several assumptions that can, or cannot, represent real-life events, which could lead to potential bias [44–49]. Also, a model is a representation of complex events, in this case, the disease process. As any model, it is subject to flaws and can lead to wrong conclusions. Therefore, it is recommended that those assumptions and the model per se be tested in the sensitivity analysis [22].

Considering this, economic studies based on real-life data are desirable so that decisions can be based on more representative data. This does not mean that economic modeling techniques are invalid, but they bring uncertainty regarding transferability of results [51].

All studies showed denosumab use was associated with lower number of SREs, longer times to develop those events, and more QALYs gained when compared with zoledronic acid users. Even though denosumab has numerous benefits compared with zoledronic acid, e.g., easier and faster administration, longer time to SREs, and no need for renal monitoring, it is more expensive. Denosumab can only be cost-effective when high willingness-to-pay thresholds are considered—it would have to be 18–26 times less costly than the estimated total drug cost, which is unlikely to happen [49].

High incremental cost-effectiveness ratios are due to the big difference of drug prices and, despite zoledronic acid's limited effectiveness, the number of SREs observed, and QALYs gained, there is not much difference in incremental effectiveness between both groups [44, 54].

Even though denosumab's superiority compared with zoledronic acid has been proven, its additional benefits are not enough to justify the incremental costs of its use, considering that denosumab's number needed to treat was 7.8 patients-year. It means that 7.8 patients would be needed to treat in 1 year to have one SRE prevented relative to zoledronic acid [55]. A recently published systematic review evaluated the cost-effectiveness of treatments for the management of bone metastasis, and came to the same conclusion when comparing bisphosphonates and denosumab. It adds small health benefits compared to

Table 3 Methodological characteristics of studies included in the systematic review

Study	Objective	Type of analysis	Compared treatments	Study perspective	Costs and sources	Outcomes and sources	Time horizon	Analyses (ICER, SA)
S1	To compare the cost-effectiveness of Dmab with ZA for the treatment of bone metastases in men with hormone-refractory prostate cancer	Markov model	Dmab (120 mg every 4 weeks) and ZA (4 mg every 4 weeks)	US third-party payer	Drug costs (CPI), SRE costs (available literature), terminal care and AE costs (US national database), and staff costs (medicare physician fee)	SRE occurrence, SRE history, disease progression, and death (available literature/phase III trials)	1 year and 3 years	ICER—total incremental cost per SRE avoided SA for drug and AE costs, discontinuation and adherence, and variation in rates of first SRE PSA considering different WTP thresholds
S2	To assess the cost-effectiveness of Dmab versus ZA in the prevention of SREs in patients with BC and bone metastases	Markov Model	Dmab (120 mg every 4 weeks) and ZA (4 mg every 4 weeks)	US third-party payer	Drug costs (CPI), SRE costs (available literature), AE costs (US national database), staff costs (Medicare physician fee), and drug monitoring costs (medicare clinical laboratory fee)	SRE type and status: no SRE, occurrence of first or subsequent SRE, and history of SRE (available literature/phase III trials)	1 year	ICER—total incremental cost per SRE avoided and per pathologic fracture avoided SA for drug and SRE treatment costs; for probability of different SRE status PSA considering different WTP thresholds
S3[a]	To assess the cost-effectiveness of Dmab compared with ZA in patients with bone metastases secondary to BC	Markov Model	Dmab (120 mg every 4 weeks) and Z A (4 mg every 4 weeks)	US payer	Drug costs (CPI); SRE costs (available literature); administration costs (national fee analyzer)	Months of survival without, with, and after SRE and death; QALY for different SREs (available literature/phase III trials)	27 months extrapolated to 60 months	ICER—incremental cost per QALY gained SA considered variations in drug price, persistence, time horizon, QOL, and survival
S4	To determine lifetime cost-effectiveness of Dmab compared with ZA in patients with bone metastases from solid tumors (CRPC, BC, and NSCLC)	Markov model	Dmab (120 mg every 4 weeks) and ZA (4 mg every 4 weeks)	US managed care	Drug costs (CPI), SRE costs (US commercial claims database), administration and monitoring costs (available literature and national fee ANALYZER), AE costs (available literature)	Occurrence of SREs, AEs, and death; QALY for SREs (available literature/phase III trials)	Lifetime	ICER—cost per QALY gained and cost per SRE avoided SA—variations in drug and administration costs, SRE costs, QALY for SREs

Table 3 (continued)

Study	Objective	Type of analysis	Compared treatments	Study perspective	Costs and sources	Outcomes and sources	Time horizon	Analyses (ICER, SA)
S5[a]	To estimate the cost-effectiveness of Dmab versus ZA in metastatic prostate cancer patients	Markov model	Dmab (120 mg every 4 weeks) and ZA (4 mg every 4 weeks)	US payer	Drug costs (CPI), SRE costs (available literature), administration and renal monitoring costs (national fee analyzer)	SRE occurrence and type, overall survival, QALY per SRE type (available literature/phase III trials)	27 months extrapolated to 60 months	ICUR—discounted incremental cost per QALY gained SA—variations in drug costs
S6[a]	To perform an economic evaluation of Dmab versus ZA in patients with bone metastases from solid tumors		Dmab (120 mg every 4 weeks) and ZA (4 mg every 4 weeks)	Greece third-party payer	Drug costs (Greek Ministry of Health Bulletin), SRE costs (Greek Ministry of Health tariffs) For ZA: administration, monitoring and staff costs and for Dmab: administration costs and health-care professional visit (Government Gazette Issues)	Efficacy and QOL decrements associated with SRE (available literature)	22.5 months for BC, 14.5 months for prostate cancer, and 9 months for other solid tumors	ICER—total cost per QALY gained and total cost per SRE avoided SA—variations in drug cost and delivery method

AE adverse event, *BC* breast cancer, *CPI* Consumer Price Index, *CRPC* castration-resistant prostate cancer, *Dmab* denosumab, *ICER* incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *NSCLC* non-small-cell lung cancer, *PSA* probabilistic sensitivity analysis, *QALY* quality-adjusted life year, *QOL* quality of life, *SA* sensitivity analysis, *SRE* skeletal-related event, *WTP* willingness-to-pay, *ZA* zoledronic acid

[a]Studies that considered ZA at generic price (50% of the current price)

Table 4 Economic data of the drugs observed in the included studies

Study	Currency	Drug cost[a]	CEA	Sensitivity analysis	Conclusion
S1	2010 US Dollars	Dmab: $1672 ZA: $953	1 year Dmab $35,3141, 0.49 SREs ZA $27,528, 0.6 SREs ICER $71,027/SRE avoided 3-Year Dmab $69,468, 1.18 SREs ZA $55,612, 1.46 SREs ICER $51,319/SRE avoided	Results were sensitive to time to first SRE, drug costs, and relative risk of having SRE associated with disease progression. Dmab is more likely to be cost-effective at higher WTP thresholds and longer time horizons	Results were favorable to ZA. Dmab was considered a costly alternative compared with ZA considering different settings
S2	2011 US Dollars	Dmab: $1673.10 ZA: $964.97	Dmab $30,033, 0.42 SREs ZA $23,511, 0.48 SREs ICER $114,628/SRE avoided	Results were sensitive to the probability of first SRE, and drug costs. The probability of Dmab being cost-effective is low even at high WTP thresholds	Results are favorable to the use of ZA considering the high costs related to Dmab. SA supports those findings
S3	2010 U. S. Dollars	Dmab: $1650 ZA $886	Dmab $30,063, 0.9406 QALYs ZA $22,956, 0.9305 QALYs ICER $697,499/QALY gained	Results were sensitive to drug prices, time horizon, time to first SRE, and utilities associated with fractures and therapeutic radiation Dmab had high likelihood of being cost-effective at WTPs ≥6,000,000 per QALY	Results showed that ZA is superior to Dmab for the prevention of SRE in patients with bone metastases from breast cancer
S4	2009–2011 U. S. Dollars	Dmab: $1650 ZA: $895.61	CRPC Dmab $76,486, 0.97QALYs ZA $69,577, 0.83 QALYs ICER $49,405/QALY gained BC Dmab $108,538, 1.76 QALYs ZA $95,087, 1.59 QALYs ICER $78,915/QALY gained NSCLC Dmab $49,068, 0.33 QALYs ZA $95,087, 0.27 QALYs ICER $67,931/QALY gained	Results were sensitive to drug costs and SRE rates Dmab had high likelihood to be cost-effective considering WTP values from $100,000 to $200,000 for CRPC and medium to high probability for BC and NSCLC	Considering all benefits associated with Dmab use and its high efficacy, this drug was considered cost-effective for the prevention of SREs in bone metastatic solid tumors
S5	2010 U. S. Dollars	Dmab: $1650 ZA: $886	Dmab $31,968, 0.9306 QALYs ZA $24,127, 0.9232 QALYs ICER $1,058,741/QALY gained	Results were robust to hazard of first SRE in Dmab group, utility value for spinal cord compression, surgery to bone, and radiation to bone At a WTP of $100,000, Dmab was not cost-effective relative to ZA	Results showed ZA is cost-effective compared with Dmab even though the latter provides more benefits
S6	2012 Euros	Dmab: ~€5261 ZA: ~€4343	Dmab as hospital therapy[b] Dmab $26,103, −0.105 QALYs lost A $8084, −0.117 QALYs lost ICER 198,944/QALY lost Generic ZA available[b] Dmab $26,103, −0.105 QALYs lost ZA $60,208, −0.117 QALYs lost ICER 268,636/QALY lost	Results were sensitive to drug prices Dmab was cost-effective at a price of € 280–290 when the drug is obtained from the healthcare fund (EOPYY) pharmacies	In none of the scenarios, Dmab was cost-effective compared with ZA In all scenarios, Dmab was not able to achieve the WTP < 30,000

AE adverse event, *BC* breast cancer, *CRPC* castration-resistant prostate cancer, *Dmab* denosumab, *ICER* incremental cost-effectiveness ratio, *ICUR* incremental cost-utility ratio, *NSCLC* non-small-cell lung cancer, *PSA* probabilistic sensitivity analysis, *QALY* quality-adjusted life year, *SA* sensitivity analysis, *SRE* skeletal-related event, *WTP* willingness-to-pay, *ZA* zoledronic acid

[a]Drug cost in unit prices

[b]Average values for BC, PC, and other solid tumors

Table 5 Adjusted ICERs to 2017 values at 3% per year according with the year of costs and outcomes measurement

Study	Year (costs)	Time (years)	Outcome	Type of cancer	Currency	ICER	Adjusted ICER
S1	2010	7	SRE/QALY	PC	USD	$71,027/$3.91 M	$87,354/$4,808,807
		4	SRE/QALY	PC		$51,319/$2.77 M	$57,760/$3,117,659
S2	2011	6	SRE	BC	USD	$114,628	$136,872
S3	2010	7	QALY	BC	USD	$679,449	$835,637
S4	2012	5	SRE	CRPC	USD	$8567	$9931
				BC		$13,557	$15,716
				NSCLC		$10,523	$12,199
			QALY	CRPC		$49,405	$57,274
				BC		$78,915	$91,484
				NSCLC		$67,931	$78,751
S5	2010	7	QALY	PC	USD	$1,088,741	$1,339,014
S6	2013	4	SRE	BC	EUR/USD[a]	€3614/$4120	€4068/$4638
				PC		€4889/$5573	€5503/$6273
				Others		€4854/$5534	€5463/$6228
			QALY	BC		€56,818/$64,773	€63,949/$72,902
				PC		€61,296/$69,877	€68,989/$78,647
				Others		€80,830/$92,146	€90,975/$103,711

BC breast cancer, *CRPC* castration-resistant prostate cancer, *EUR* Euros, *ICER* incremental cost-effectiveness ratio, *NSCLC* non-small cell lung cancer, *QALY* quality-adjusted life years, *SRE* skeletal-related events, *USD* United States Dollars

[a]Conversion based on July 1st, 2017 currencies, available from: http://www.xe.com/currencycharts/?from=EUR&to=USD&view=1Y

the additional costs it imposes, which makes denosumab unlikely to be cost-effective [56].

Zoledronic acid's patent expired in 2013. Since then, generic versions of this medication have been manufactured and sold at lower prices in developing and developed countries [49]. In three analyses, generic zoledronic acid prices were estimated before patent expiration. Only the results of Stopeck et al. [47] were favorable to denosumab and represented cost savings, even though it did not consider ZA's patent expiration. However, in studies that considered this change in the scenario (S3, S5 and S6), denosumab was not cost-effective in all cases [46, 48, 49], meaning that the prices of generic zoledronic acid could potentially result in limitations for denosumab use in the prevention and management of SREs in metastatic bone disease.

Also, decision makers should also consider medium- and long-term projections. Two studies considered a 1-year horizon; two analyzed 27 months, extrapolated to 5 years; one had different horizons for different types of cancer; and only one study considered a lifetime horizon. Curiously, only the latter found that denosumab has favorable cost-effectiveness when compared with zoledronic acid, even though the authors considered higher willingness-to-pay thresholds that would hardly be accepted. Added to that, budget impact analysis should be conducted to verify if those options are economically viable and sustainable over the years [57].

One fact that drew attention is that all studies were funded by pharmaceutical companies, more specifically, Novartis Industry and Amgen Inc., which could raise important ethical issues and conflicts of interest.

The influence that industry sponsorship may have on the study results remains unclear. Different studies were conducted to investigate this question. Two systematic reviews showed positive correlation between pharmaceutical industry-sponsored studies and favorable results to the sponsor [58, 59].

The authors of those studies discussed possible reasons for those results: the pharmaceutical industry tends to sponsor drug studies that have evidence of superiority; the possibility of influencing protocols to the company advantage; data interpretation favors the sponsor; and publication bias. Among the hypotheses was that pharmaceutical industry-sponsored studies had inferior methodological quality. However, the systematic reviews showed their methods were as good as the other studies, sometimes even better [58, 59].

Considering the potential bias in pharmaceutical industry-sponsored studies, careful considerations should be taken when analyzing their results and applicability to the context of interest.

Also, in economic studies, reminding that interpretation about the cost-effectiveness of a strategy relative to other depends on the willingness-to-pay thresholds adopted by an institution is important. For the United States, some suggest the threshold of $50,000 per quality-adjusted life year (QALY), while others propose higher thresholds [60].

In the cost-effectiveness analyses that compared denosumab with zoledronic acid, the former had favorable cost-effectiveness for the prevention of SREs, but it provides two ICER values: costs per QALY gained ($49,405–$78,915, depending on the type of cancer) and costs per SRE avoided ($8567–$13,557) [46]. If values up to $50,000 are acceptable, then denosumab would be considered not cost-effective, whereas if higher thresholds are adopted, then the conclusion of this study would be appropriate.

We calculated adjusted ICERs of the base cases for 2017 considering inflation rates of 3% per year. These ratios were, as expected, higher than past values, considering the effects of inflation on costs and benefits. For most of the studies, ICERs per SRE avoided or per QALY gained remain above the acceptable threshold limits considered, and the authors concluded that ZA is superior to denosumab despite all its advantages (S1, S2, S3, and S6).

Only in study S4, incremental costs per QALY gained for castration-resistant prostate cancer patients were below the most commonly adopted WTP values (US$50,000.00), but if one would consider all types of solid tumor in a cluster, incremental costs per QALY gained would be higher than WTP thresholds. In the same study, denosumab was considered cost-effective relative to zoledronic acid at WTP between $100,000 and $200,000. S6, on the other hand, conducted in a different scenario analysis, considered different drug prices, medical coverage and administration method, but none of the ICERs achieved values below $50,000. However, stretching WTP thresholds to $100,000, denosumab would be cost-effective for SRE prevention in bone and prostate cancer patients.

These two studies are clear examples that show the need for caution when collecting data and analyzing them to either provide information or for decision-making. Data are presented in different ways and parameters can be diverse, which can lead to misunderstandings and erroneous conclusions.

Even though previous systematic reviews did not include as many studies as ours [43] or was conducted with a different sample [41] or had a different objective but presented cost-effectiveness analysis [40], those studies came to the same conclusion: denosumab is unlikely to be cost-effective, mainly because of denosumab's high costs despite of its advantages—ease of use, no need for renal monitoration, less acute phase reactions, among others—, and its proven superior effectiveness relative to zoledronic acid.

No standardized tool has been established to assess methodological quality of the results. Different approaches are available for this evaluation, but none of them is considered a gold standard. The approaches are based on key issues all economic evaluations should comprise: clear description of the problem and of the objective, study perspective, time horizon, detailed description of alternatives, proper identification and measurement of all relevant costs and outcomes, time adjustment, incremental and sensitivity analyses, and generalizability [61, 62].

In this review, the methodological quality of the included studies was assessed using the JBI critical appraisal tool of economic studies. Most part of the studies fulfill all requirements, except for one, in which it is not clear whether time adjustment was considered (S6), which, can jeopardize the results in all scenarios. Again, the fact that all studies were based on existing literature data brings uncertainty regarding the generalizability of the results. Thus, in the methodological evaluation, for all studies, this item was considered "unclear".

This systematic review was the first to provide more recent data solely regarding the use of denosumab compared with zoledronic acid for the treatment of bone metastases from solid tumors considering recent changes in the pharmaceutical market. Previous reviews included a restricted sample (prostate cancer only), had different objectives (analyze methodological characteristics), and did not include most recently published studies.

The analyses of the retrieved evidence highlight the importance of developing new economic analyses based on observational data, representative of real-life conditions, and that consider the issue of the zoledronic acid patent expiration and the use of generic forms for the treatment of bone metastases from solid tumors.

Conclusion

The present study found only six economic studies that compared denosumab with bisphosphonates for patients with bone metastases from solid tumors, and only zoledronic acid was used. Results regarding the cost-effectiveness of the bone-targeted therapies remain mixed, but 83.4% of the reviewed studies showed that denosumab has unfavorable cost-effectiveness compared with zoledronic acid mainly because of denosumab's high costs. All results were based on clinical trial data and other evidence from literature, which means that the analyses could have been subjected to data restrictions and numerous assumptions that could lead to potential bias. New economic studies based on real-life data and that also compares denosumab with bisphosphonates other than zoledronic acid are needed.

Compliance with ethical standards

Human/animal rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors have no conflicts of interest to declare.

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