Bone 59 (2014) 105–113

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Original Full Length Article

Denosumab: A cost-effective alternative for older men with osteoporosis from a Swedish payer perspective

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ARTICLE INFO

Article history:
Received 14 March 2013
Revised 30 October 2013
Accepted 1 November 2013
Available online 12 November 2013

Edited by: David Fyhrie

Keywords:
Male osteoporosis
Cost-effectiveness
Denosumab
Sweden
Fracture

ABSTRACT

Objective: To assess the cost-effectiveness of denosumab versus other treatments in men with osteoporosis who are ≥75 years old from a payer perspective in Sweden.
Methods: A lifetime cohort Markov model was developed with seven health states: well, hip fracture, vertebral fracture, other osteoporotic fracture, post-hip fracture, post-vertebral fracture, and dead. During each cycle, patients could have a fracture, remain healthy, remain in a post-fracture state or die. Background fracture risks, mortality rates, persistence rates, utilities, medical and drug costs were derived using published sources. Estimates of fracture efficacy were drawn from available studies in post-menopausal osteoporotic (PMO) women as BMD improvements have been shown to be similar across male osteoporosis (MOP) and PMO populations, and a recent clinical trial suggested that the fracture risk reduction from bisphosphonate therapy in men is similar to that seen in women in comparable studies. Lifetime expected costs and quality-adjusted life-years (QALYs) were estimated for denosumab, generic alendronate, generic risedronate, ibandronate, zoledronate, strontium ranelate and teriparatide. On average, patients in the model were 78 years old, with bone mineral density T-score at the femoral neck of −2.12. Prevalent vertebral fractures were present in 23% of patients. In the base-case, the model assumed that patients would experience treatment-related effects up to 2 years after discontinuation. Costs and QALYs were discounted at 3% annually. Extensive sensitivity analyses were conducted.
Results: Total lifetime costs for denosumab, alendronate, strontium ranelate, zoledronate, risedronate, ibandronate and teriparatide were €31,004, €33,731, €34,788, €34,796, €34,826, €35,983 and €37,461, respectively. Total QALYs were 5.23, 5.15, 5.15, 5.17, 5.13, 5.12 and 5.22, respectively. Compared to other treatments, denosumab had the lowest costs and highest QALYs. In the one-way sensitivity analyses, when compared to alendronate (next least expensive strategy), the ICER for denosumab was most sensitive to the relative risk of hip fracture on denosumab. The probability of denosumab being cost-effective compared to the other treatments at a threshold of €66,000/QALY was 96.1%.
Conclusion: Denosumab dominated all comparators, including generic bisphosphonates, in the treatment of osteoporosis in men who were ≥75 years old in Sweden.

Introduction

In Sweden, 70,000 osteoporotic fractures occur per year; 27% are hip fractures and 23% are vertebral fractures [1]. Osteoporotic fractures are associated with an increased risk of institutionalization and decreased mobility [2]. Age increases the 10-year probability of osteoporotic fracture [3], as well as the economic burden of a fracture, which is highest in patients over 75 years old [4].

Osteoporosis affects 1 in 5 men over the age of 50, worldwide [2] and can lead to hip fractures, which incur significant direct medical costs. Although osteoporosis is less common in men than in women, 25–30% of all hip fractures worldwide are in men and the risk of mortality after osteoporotic fractures is greater in men than in women. Men with a previous vertebral fracture have 4 times the risk of a hip fracture compared to

Abbreviations: ADAMO, A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of DenosumAb 60 mg every six months versus placebo in Males with Osteoporosis; BMD, Bone mineral density; DAPS, Denosumab Adherence Preference Satisfaction; EMA, European Medical Agency; EQ-5D, EuroQOL-5 Dimension; FIT, Fracture Intervention Trial; FREEDOM, Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months; HALT, Hormone Ablation Bone Loss Trial; ICER, Incremental cost-effectiveness ratio; IV, Intravenous; LTC, Long-term care institution; LY, Life-year; MOP, Male osteoporosis; NICE, National Institute for Health and Care Excellence; PMO, Post-menopausal osteoporosis; PSA, Probabilistic sensitivity analysis; QALY, Quality-adjusted life-year.

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http://dx.doi.org/10.1016/j.bone.2013.11.002

the overall population [5]. The number of hip fractures is increasing in both men and women, and by 2025 it is estimated to be 1.1 million in men [6].

There are many pharmacological treatments, including bisphosphonates, teriparatide and strontium ranelate that have been studied or indicated for use in men with osteoporosis. Denosumab, administered as 60 mg subcutaneously every 6 months, is indicated for treatment of postmenopausal women with osteoporosis at high risk of fracture and to increase bone mass in men with osteoporosis at high risk of fracture. In an international, multi-center, randomized, double-blind placebo-controlled study (FREEDOM — **F**racture **RE**duction **E**valuation of **D**enosumab in **O**steoporosis Every 6 **M**onths-trial [7]) of postmenopausal women with osteoporosis, denosumab significantly reduced the risks of new vertebral, non-vertebral, and hip fractures vs. placebo at 3 years. The efficacy of denosumab in men aged 30–85 years with low BMD (bone mineral density) at the lumbar spine or femoral neck was evaluated in a phase 3, double-blind, placebo-controlled clinical study (**A** multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of **D**enosum**Ab** 60 mg every six months versus placebo in **M**ales with **O**steoporosis — ADAMO-trial [8]). Patients received either denosumab or placebo for 12 months. All patients continued for an additional 12 months on open-label denosumab. Results showed that at 12 months, denosumab-treated patients had significantly greater BMD gains at the lumbar spine, total hip, femoral neck, trochanter and distal radius than placebo-treated patients. Therefore, denosumab could represent an important therapeutic approach to treating male osteoporosis (MOP).

Since the resources within the health care sector are scarce, evidence of safety and efficacy is no longer sufficient to guarantee good access to therapies — evidence of economic value is also required. Denosumab has been demonstrated to be a cost-effective strategy compared to bisphosphonates and strontium ranelate in postmenopausal osteoporotic (PMO) women in both Sweden and the US [9,10]. In this analysis, the cost-effectiveness of denosumab in osteoporotic men was evaluated from a payer's perspective in Sweden.

Methodology

A previously published lifetime Markov cohort model in PMO women was adapted to examine the cost-effectiveness of denosumab compared to generic alendronate, generic risedronate, ibandronate, zoledronate, teriparatide, and strontium ranelate in MOP patients in Sweden [9]. The cost-effectiveness analyses focused on men with age 75 years and older, as fracture is more common in this age group and these individuals are most vulnerable to the debilitating effects of fracture. These characteristics were reflective of a subgroup analysis of the elderly population in ADAMO-mean age 78 years, with a femoral neck BMD T-score of −2.12 and prevalent vertebral fractures in 23% of patients [8,11].

Fig. 1 illustrates the structure of the Markov model. Patients in the model enter in the “well” health state. During each Markov cycle (i.e. every six months) patients in the cohort have a probability of sustaining a fracture, remaining healthy or dying. Patients in the cohort who experience a fracture, depending on fracture type, may transition to the hip fracture, vertebral fracture or “other” osteoporotic fracture health state. After one year in a given fracture state, the patients can a) sustain a new fracture, b) move to the post-fracture state (either post-hip or post-vertebral fracture, depending on the previous health state), c) move back to the “well” state (“other” fracture patients only) or d) die.

Patients in the post-vertebral fracture state can either stay in this state, experience a new vertebral fracture, experience a new hip fracture or die. From the post-hip fracture state, patients can either remain in the post-hip fracture state, sustain another hip fracture or die.

Model estimation

Treatment efficacy

In the absence of well-powered trials evaluating clinical fracture risk reduction in MOP, we used assumptions concerning drug efficacy derived from trials in PMO women to estimate the anti-fracture efficacies of the osteoporosis treatments selected. The rationale for taking this approach is based on several factors. First, BMD improvements in response to interventions have consistently been shown to be similar across MOP and PMO populations [8,12–15]. For instance, in patients on denosumab who were ≥75 years of age, percentage change from baseline to month 12 in lumbar spine BMD was comparable between women in the FREEDOM (placebo: 0.7 (95% CI −0.1–1.4) vs. denosumab: 4.8 (95% CI 4.1–5.6)) and men in the ADAMO (placebo:1.0 (95% CI −0.5–2.5) vs. denosumab: 4.8 (95% CI 3.3–6.4)) trials respectively [8,11]. Furthermore, it's reasonable to assume that similar changes in BMD in men and women will reflect similar effects on fracture risk reduction, and according to the European Medical Agency (EMA) guidelines, a therapy approved in PMO women may use a bridging study for MOP approval, provided that the study is at least 1 year in duration and has similar dosing regimens, fracture risks, and BMD changes [16]. In fact, a recent clinical trial suggested the fracture risk reduction from bisphosphonate therapy in men is similar to parallel studies in women [17]. Therefore, in the current study, the fracture risk reductions were derived from the PMO trials for use in this MOP analysis (see Table 1). In the absence of evidence for fracture reduction for a particular treatment at a particular skeletal site, 0% fracture risk reduction was assumed.

Persistence

The risk of treatment discontinuation within the first four years for the comparators was estimated using persistence data obtained from Landfeldt et al. [18]. Persistence rates were based on a composite estimate of patients taking alendronate, risedronate, or strontium ranelate (Table 2). The persistence rate for denosumab was estimated based on DAPS (**D**enosumab **A**dherence **P**reference **S**atisfaction) [19], which is a multi-center, randomized, cross-over, open-label study to evaluate the adherence, preference, and satisfaction of denosumab and alendronate in postmenopausal women with low bone mineral density. A total of 250 subjects were randomized to alendronate (weekly dosing) or denosumab every 6 months. At month 12, patients were assigned to the opposite (cross-over) treatment, and followed for an additional 12 months. At the end of month 12, patients on denosumab were 50% less likely to discontinue treatment ($p = 0.029$) than those given alendronate. Thus, the absolute discontinuation rate for denosumab was estimated by multiplying 0.5 by the discontinuation rate for bisphosphonates identified in the literature [19]. The other injectable osteoporosis treatments, teriparatide and zoledronic acid, were assumed to have the same persistence as denosumab (Table 2).

Although teriparatide is a daily injection (compared to twice yearly denosumab and annual zoledronic acid), Landfeldt et al. [18] reported that about 70.3% (CI 95 64.0–75.8%) of patients from the Swedish Prescribed Drug Register were likely to be persistent for 1 year. While Landfeldt et al. stated that there was a marked decline in teriparatide persistence after 18 months of treatment, no further data was provided. Two other studies also reported persistence of teriparatide [20,21], however they did not report data in the Swedish setting and beyond 18 months.

In the model, the proportion of patients who are persistent on denosumab in the model at the end of 1 year is 71.6%; similar to the persistence rate for teriparatide reported by Landfeldt et al. [18] Therefore, in the model, persistence for teriparatide was set equal to denosumab.

Based on their dosing regimens, it was assumed that patients on denosumab (given twice per year) and zoledronic acid (given once per year) were persistent for at least 6 months, while patients on oral