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ORIGINAL ARTICLE

Combining fracture outcomes in phase 3 trials of osteoporosis: an analysis of the effects of denosumab in postmenopausal women

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Abstract

Summary This paper explores use of metrics that combine fracture outcomes that add power to phase 3 studies and provide a surrogate outcome for regulatory agencies.

Introduction The aim of this study was to develop an analytic framework that would combine information from all fracture outcomes (including radiographic vertebral fractures) in phase 3 studies to provide a metric for the assessment of treatment efficacy.

Methods Data from the phase 3 study of denosumab were used as an exemplar comparing the effects of active intervention with placebo on the risk of all fractures associated with osteoporosis. Fracture outcomes were assigned utility weights drawn from the published literature and applied to age-specific health state values of the general population. For each fracture outcome in each arm of the study, cumulative disutility was computed to serve as the principal end point. The hypothesis tested was that treatment with denosumab results in a significant reduction in mean fracture-related disutility.

Results Treatment with denosumab was associated with significantly lower utility loss compared with placebo. For patients treated with denosumab, mean utility loss was 42% less than with placebo (4.5 vs. 7.5 QALYs/1000 patient years, respectively, $p < 0.001$).

Conclusions Denosumab significantly decreased utility loss. The use of metrics that combine fracture outcomes may provide added power to phase 3 studies and provide a surrogate outcome for regulatory agencies.

Keywords Denosumab · Disutility · Fracture · Phase 3 study · Quality of life years

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Introduction

Current regulatory requirements for the development of treatments for osteoporosis in Europe and the USA demand that studies of efficacy in osteoporosis report vertebral and nonvertebral fracture outcomes separately [1, 2]. One reason is that the methods of data acquisition differ. Thus, clinical fractures are recorded by the date on which they occur, whereas vertebral fractures assessed by semi-quantitative morphometry are recorded by the date of the radiograph, but the incident fracture may have occurred at any time between radiographs. From a clinical perspective, the distinction is a little artificial in that both vertebral and nonvertebral fractures contribute to the morbidity and indeed mortality of osteoporosis [3–11]. There is, therefore, clinical interest in combining fracture outcomes in order to define an integrated estimate of efficacy.

A limitation of combining fracture endpoints is that there may be preferential drivers of efficacy. For example, the major

effect of some interventions is on vertebral fracture risk, with a lesser effect on nonvertebral fractures. This limitation can be overcome by weighting fracture outcomes by their disutility which would accord much more weight to hip fracture outcomes than, for example, to morphometric vertebral fractures [12, 13]. The approach is similar in principle to the use of quality of life years (QALYs) gained in health economic evaluation and the converse, disability adjusted life years (DALYs) lost as used by the WHO and the World Bank to quantify the burden of disease [8, 9, 14, 15]. The reduction of multiple endpoints to a single outcome variable such as disutility has the potential to increase the power of phase 3 studies and to permit comparisons of efficacy across treatments (and across diseases).

The aim of this study was to develop an analytic framework that combined all disutility-weighted fracture outcomes. In this context, we examined the effects of denosumab in the phase 3 "Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months" (FREEDOM) study.

Methods

FREEDOM study

The primary data of the FREEDOM study were used. Details of the study are published elsewhere [16]. In brief, this multinational study of efficacy included women from Canada, Europe, Latin America, South America, and the USA. FREEDOM was a double-blind, randomized, placebo-controlled trial including 7808 women between the ages of 60 and 90 years (mean 72 years) who had a BMD T-score of less than −2.5 at the lumbar spine or total hip but not less than −4.0 at either site. All women received supplements containing at least 1000 mg of calcium daily with vitamin D (400 to 800+ IU daily), the latter depending on the baseline serum 25-hydroxyvitamin D level. Women were randomly assigned to receive either 60-mg denosumab or placebo subcutaneously every 6 months for 36 months. The primary endpoint of the study was new vertebral fracture, assessed on annual spine radiographs using the Genant semiquantitative method for diagnosis. Secondary endpoints included nonvertebral and hip fractures.

Compared with placebo, denosumab reduced the risk of new radiographic vertebral fracture (risk ratio, 0.32; 95% confidence interval (95% CI) = 0.26–0.41), clinical vertebral fracture (hazard ratio, 0.31; 95% CI = 0.24–0.63), hip fracture, (hazard ratio, 0.60; 95% CI = 0.37–0.97), and nonvertebral fracture (hazard ratio, 0.80; 95% CI = 0.67–0.95) [16]. No data on all clinical fractures were reported [16].

In a model including time since study entry, age, and FRAX major osteoporotic fracture probability, treatment with denosumab was associated with a significant decrease in clinical osteoporotic fractures (relative risk reduction = 32%; 95% CI = 20–42%; $p < 0.001$) [17]. Clinical vertebral fractures were included in this estimate but not radiographic vertebral fractures.

Fracture outcome variables

For the present analysis, the primary outcome of interest was all fractures considered to be related to osteoporosis [12]. These included clinical vertebral fractures, vertebral fractures assessed by semiquantitative morphometry, and fractures of distal forearm, pelvis-sacrum, ribs-sternum, clavicle, humerus, proximal femur, tibia, and fibula; fractures of the hands, ankle, feet, skull, and facial bones were excluded.

In order to determine the feasibility of combining all vertebral and other fracture outcomes, we first tested the assumptions made concerning the date of an incident morphometric fracture since the incident fracture may have occurred at any time between two sequential (approximately yearly) radiographs. In one analysis, we assumed that the date of the radiograph to be the date of fracture, and in a second comparative analysis, we assumed that the time of a fracture event would be at the mid-interval between two consecutive radiographs. The models comprised as follows: (1) constant, (2) the time since entry, (3) current age, (4) treatment, and (5) treatment × current time.

The beta coefficients were very similar when comparing the two models, so that we used the mid-interval between two consecutive radiographs as the date of vertebral fracture.

Utility weighting

Cumulative loss of utilities was calculated using utility multipliers derived from the EQ-5D 3 Levels descriptive system (EQ-5D 3L). The EQ-5D is a generic quality of life (QoL) instrument that is applicable to a wide range of health conditions and provides a simple but robust health profile that can be translated to health state utility values (HSUVs) [18]. The instrument has shown good sensitivity to osteoporotic fracture, has been recommended for inclusion in hip fracture trials [19], and is widely used in health economic assessments [18]. The patient administered questionnaire describes health in five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. For topics within each dimension, patients specify their state on a three-level scale, comparable to no difficulty, some difficulty, and great difficulty, resulting in 243 possible combinations.

Accumulated quality of life (QoL) loss and QoL multipliers were those derived where possible from the

International Costs and Utilities Related to Osteoporotic Fractures Study (ICUROS), which is the largest prospective observational study on QoL consequences of osteoporotic fracture conducted to date with an analysis that included more than 3000 fracture cases [20]. Empirical data were available for most fracture sites [21]. For "other femoral fracture," it was assumed that these had the same utility loss as fractures at the hip. For fractures of the clavicle, scapula, or sternum, we used previously published utility values [12]. Utility loss for morphometric vertebral fractures was set at one-third of that for clinical vertebral fractures [22].

The multipliers for utility loss were applied to health state values (HSVs) published for the UK general population [23], since country-specific value sets were not available for most countries included in FREEDOM study. The UK value set is considered to be the most robust and is recommended by the EUROQoL group in the absence of country-specific value sets [18]. The assumption implies that a patient has a normal health state value for age at entry to the study. This is unlikely to be correct due to the high prevalence of co-existing morbidity in women with osteoporosis. However, the assumption is applied to both placebo and actively treated patients and is unlikely, therefore, to bias the comparative effects of denosumab versus placebo.

Thereafter, multipliers were applied for each subsequent eligible fracture that occurred each day for the duration of follow up. For example, the utility loss multiplier following a clinical vertebral fracture would be 0.27 on the first year and 0.13 in the second year and subsequent years. In the case of death, no utility loss was ascribed, since the aim of the study was to determine the consequences of the fracture in individuals who survived. For the same reason, side effects were not included.

Statistical analysis

The cumulative loss of utility was calculated for patients taking placebo and denosumab. Fisher's permutation test was used to test the difference between the two treatment groups according to utility loss. Utility loss was also expressed as QALY loss/1000 patient years.

The p values of the current comparison between denosumab and placebo were used to derive sample sizes of a future study of equal patient numbers in each arm with a power of 80% to detect a significant ($p < 0.05$) difference in disutility. These sample sizes were compared with those derived from fracture outcomes previously published by Cummings et al. [16]. In the case of very small p values, e.g., $p < 0.001$, the exact p value was calculated from the hazard ratio and confidence interval given in Cummings et al. [16]. The assumption for the power calculation is that all conditions are the same in the next study (i.e., similar population, distribution of the differences between the treatment groups, risk of fractures, and duration of study).

Results

The baseline characteristics of the 7808 women are shown in Table 1. There were no differences between the two study groups at entry, including baseline FRAX probabilities. Patients were followed up for 10,740 person years in the

Table 1 Baseline characteristics of the study population including prevalence (%, actual numbers in parentheses) of the clinical risk factors

	Placebo ($N = 3906$)	Denosumab ($N = 3902$)
Age (years)	72.3 ± 5.2	72.3 ± 5.2
BMI (kg/m^2)	25.9 ± 4.2	26.0 ± 4.1
Femoral neck BMD (g/cm^2)	0.678 ± 0.104	0.679 ± 0.106
Femoral neck T-score	− 2.2 ± 0.7	− 2.1 ± 0.7
Prior fracture (%)	50 (1953)	51 (1985)
Parental hip fracture (%)	10 (376)	10 (378)
Alcohol ≥ 3 units daily (%)	1 (57)	2 (67)
Current smoking (%)	10 (379)	9 (351)
Secondary osteoporosis (%)	22 (869)	21 (837)
10-year FRAX probability (%)		
Major osteoporotic fracture with BMD	15.1 (10.4–21.4)	15.1 (10.4–21.7)
Major osteoporotic fracture without BMD	16.7 (11.4–24.3)	16.9 (11.2–24.0)
Hip fracture with BMD	4.8 (2.5–8.7)	4.8 (2.5–8.7)
Hip fracture without BMD	6.1 (3.5–10.7)	6.2 (3.5–10.6)

Age, BMI, and BMD are expressed as mean and SD and 10-year probabilities of a major osteoporotic fracture (%) or hip fracture (%) are medians (interquartile limits)

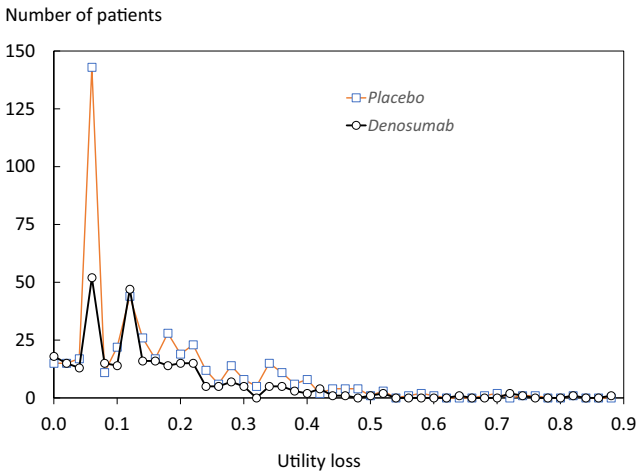

Fig. 1 The distribution of utility loss in women sustaining incident fractures in the two treatment groups. Note that the scale on the x-axis is in intervals of 0.02. Thus, 0 on the x-axis refers to the interval $0 < x < 0.02$

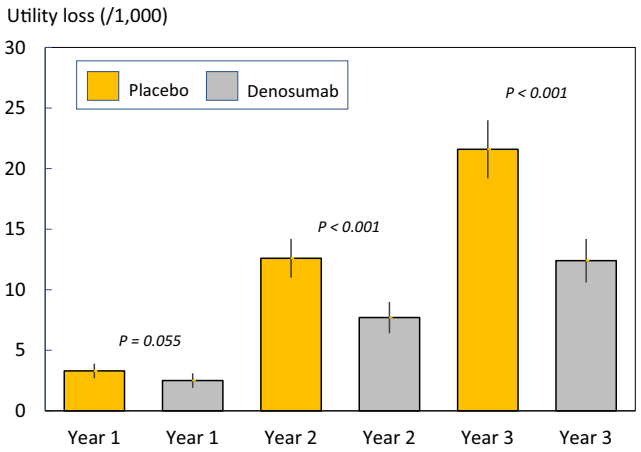

Fig. 2 Mean cumulative utility loss per 1000 persons (with 95% confidence intervals; CI) for the two treatment groups at the end of year 1, 2, and 3

placebo arm and 10,806 person years in the case of denosumab. There were 90 and 70 deaths in the placebo and denosumab arms, respectively.

Fracture-related utility loss was confined to a minority of patients. 3559 women (91%) of the placebo-treated patients group had no utility loss during the course of the study, and for denosumab, the figure was 3648 (93%). The distribution of utility loss in those experiencing fractures is shown in Fig. 1. The peak for values 0.06–0.08 were individuals sustaining only a radiographic morphometric fracture.

Utility loss was significantly less (42% lower) during treatment with denosumab than with placebo (Table 2). Utility losses were less marked when morphometric vertebral fractures were excluded but the difference between denosumab and placebo treated patients persisted (38% lower). The difference in disutility between the treatment groups was of borderline significance at the end of the first year of observation but became highly significant after 2 and 3 years (Fig. 2).

In the context of new intervention studies, the sample sizes required to have 80% power is shown in Table 3 for utility loss and fracture outcomes at specific sites. Sample sizes of less than 3000 are adequate in the case of utility loss and vertebral fracture but larger sample sizes would be necessary for other fracture outcomes.

Table 2 Mean utility loss per 1000 patients (with 95% confidence intervals; CI) for the two treatment groups

	Placebo		Denosumab		P*
	Mean	95% CI	Mean	95% CI	
All osteoporotic fractures					
Utility loss/1000	21.7	19.3–24.1	12.5	10.7–14.3	< 0.001
Excluding morphometric vertebral fracture					
Utility loss/1000	18.4	16.1–20.7	11.4	9.6–13.2	< 0.001

*Two-sided, Fisher's permutation test

Discussion

The present study provides a framework whereby efficacy can be evaluated by utility loss in phase 3 intervention studies of osteoporosis in addition to the more traditional endpoints. The approach has the merit of providing an integrated estimate of efficacy that combines all fracture outcomes of clinical relevance, weighted according to the utility loss occasioned by each fracture event. In the present study, treatment with denosumab was associated with a 42% lower loss of utility than treatment with placebo. A further characteristic is that the application of the technique does not require larger sample sizes than those needed for specific fracture outcomes. Indeed, the converse is true for several fracture outcomes. For example, the sample size required to determine a significant effect of denosumab on hip fracture with 80% power would be in the order of 15,000 patients whereas for a utility outcome occasioned by hip fracture, less than 3000 patients would be required.

The question arises of the potential impact on the regulatory environment. In the context of osteoporosis, pharmaceutical companies are directed away from investments in osteoporosis, in part because of the large sample sizes, long follow-up, and heavy financial penalties. Moreover, the advent of effective agents for the treatment of osteoporosis has led to the view that placebo-controlled trials to test new agents for efficacy are no longer appropriate since proven treatments are available. Sponsors and regulatory agencies have to consider studies of equivalence or non-inferiority, which raise more problems than they resolve [24]. For these reasons, much attention has been directed to the way clinical trials might be

Table 3 Rank order of probability (p) values for various fracture-related outcomes comparing denosumab with placebo and sample size needed in a new study to achieve 80% power using 5% significance level

Study outcome	p	Sample size
New morphometric vertebral fracture	6.0E-27[a]	< 2733
Utility loss (with morphometric vertebral fracture)	2.0E-10	< 2733
Clinical vertebral fracture	1.6E-7[a]	< 2733
Utility loss (without morphometric vertebral fracture)	8.6E-7	< 2733
Multiple morphometric vertebral fracture	1.5E-4[a]	4216
Nonvertebral fracture	0.01	9213
Hip fracture	0.04	14,523

[a] Calculated from hazard ratio and confidence interval given in [16]

less burdensome, for example, with the use of changes in bone mineral density as a surrogate for fracture [25, 26].

Several meta-analyses of phase 3 studies have described the relationship between changes in BMD and changes in fracture risk [27–30]. The most recent assessed 38 placebo-controlled trials and a meta-regression indicated that greater improvements in total hip, femoral neck BMD, and lumbar spine BMD were all strongly (sic) associated with a greater reduction in vertebral and hip fracture [29, 30]. The authors concluded that the regression provides compelling evidence that improvements in BMD with osteoporosis therapies may be useful surrogate endpoints for fracture in trials of new therapeutic agents. Whereas the conclusion that increases in BMD are associated with decreases in fracture risk is strong, the claim for the adequacy of BMD changes as a surrogate for fracture outcomes is wanting due to the poor coefficients of determination. For a decrease in hip fracture risk, for example, r^2 ranged from 22 to 48% for the association with changes in lumbar and total hip BMD, respectively. Thus, if changes in BMD were used as a surrogate marker for antifracture efficacy, the confidence interval of estimated fracture reductions would be appreciable such that no new treatments could be confidently compared with the current therapeutic armamentarium. The strategy also does nothing to alleviate the expense incurred in requiring BMD tests.

Against this background, the application of cumulative utility losses may provide an efficient way to optimize phase 3 trials with data of clinical relevance. Indeed, utility losses might be used to gain registration with accompanying trends for specific fracture outcomes. Moreover, the cost of BMD testing might additionally be avoided.

The use of utilities is not new in the sense that it is a component of health utility assessment to assess the cost-effectiveness of interventions [31, 32]. Such health economic analyses are traditionally applied after the completion of phase 3 studies, most often to justify reimbursement. In contrast, the present study incorporates utility losses as an endpoint. There are, however, some differences in their use. First, in the present study, no utility loss was ascribed in the case of death, whereas this a component of cost-utility analysis. The rational for the departure is that the aim of the present study was to solely to determine the impact of the intervention on the fracture outcome. For the same reason, side-effects were not included. Second, we incorporated all relevant fractures, whereas in the case of multiple concurrent fractures, only the fracture with the highest utility loss is usually considered in heath economic analyses.

The present study has a number of limitations. We used population health-state values from the UK, and these are likely to differ in the different countries that were recruited to the FREEDOM trial. The assumption is also made that a patient has a normal health state value for age at entry to the study. This is unlikely to be correct due to the high prevalence of co-existing morbidity in women with osteoporosis. However, the limitations are applied to both placebo and actively treated patients and is unlikely, therefore, to bias the comparative effects of denosumab versus placebo.

In addition to validation in other phase 3 settings, future work might include assigning a monetary value to disutility. The value of a QALY may differ between and within countries due to a number of factors including degree of prosperity, cultural attitudes, and the opportunity costs of resources devoted in obtaining a marginal QALY. Previously used approaches set the value of a QALY at 2 × gross domestic product (GDP) per capita for the reference country [33, 34]. Knowing the monetary value of a marginal QALY, the cost of intervention and the marginal QALY gains with treatment will permit a conservative estimate of the net societal cost of intervention.

We conclude that denosumab significantly decreased utility loss. The use of metrics that combine fracture outcomes may provide added power and flexibility to phase 3 studies.

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Compliance with ethical standards

Conflicts of interest E Liu, L Vandenput and H Johansson have no competing interests to declare.

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