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Denosumab in osteoporosis-related fractures
A critical appraisal of the FREEDOM trial

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abstract

Objective: to carry out a critical appraisal of the FREEDOM trial and discuss the information provided in the prevention of osteoporosis-related fractures. **Methods:** critical appraisal of both data published in the article by Cummings SR, and available data on the trial in the FDA and EMA's assessment reports. **Results and conclusions:** denosumab has shown efficacy vs placebo in the reduction of morphometric vertebral fractures, an endpoint of dubious clinical relevance. Data on prevention of hip fractures are inconclusive. Safety data published do not concur with the drug information available from regulatory agencies. Due to the exclusion criteria in the trial, the results are not applicable to women previously treated with bisphosphonates. Given the high risk of bias of the FREEDOM trial, the conclusions derived from this study should be considered with precaution. Furthermore, the serious irregularities found in the trial inspections raise concern on the veracity of the published data. **Key words:** denosumab, osteoporosis, bone fracture, RANKL ligand.

Introduction

Denosumab is a drug recently introduced in the market for the management of osteoporosis in postmenopausal women with a high risk of fracture. The indication is based on a single trial known as the FREEDOM trial. The drug has also been approved in the management of bone loss related to hormone suppression in men with prostate cancer and high risk of fracture.

This drug is a monoclonal antibody which binds to the RANKL ligand on the surface of osteoclasts and inhibits their formation, activity and survival. This leads to a reduction in bone resorption. The mechanism of action is different to that of bisphosphonates, but ultimately they both produce the same results, that is the inhibition of the osteoclasts and bone turnover.

The aim of this paper is to carry out a critical appraisal of the FREEDOM trial[1] and discuss the information provided in the prevention of osteoporosis-related fractures. The information considered includes both data published in the article by Cummings SR, and available data on the trial in the FDA and EMA's assessment reports.

Description of the FREEDOM trial

Research question
Is denosumab effective in the reduction of vertebral fractures in comparison to placebo?

Design
Randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial with an average study period of 36 months.

Setting
182 centres in the USA, Europe, Australia, New Zealand, and Latin America.

Patients
7,868 women aged 60 to 90 years with a bone mineral density T-score of less than –2.5 at the lumbar spine or total hip were included. Women were excluded if:
· They had conditions that influence bone metabolism or had taken oral bisphosphonates for more than 3 years. If they had taken bisphosphonates for less than 3 years, they were eligible after 12 months without treatment.
· They had used intravenous bisphosphonates, fluoride, or strontium for osteoporosis within the past 5 years.
· They had used parathyroid hormone or its derivatives, corticosteroids, systemic hormone-replacement therapy, selective estrogen-receptor modulators, or tibolone, calcitonin, or calcitriol within 6 weeks before study enrollment.
· They had a bone mineral density T score of less than –4.0 at the lumbar spine or total hip.
· They had any severe (or more than two moderate) prevalent vertebral fractures

Baseline characteristics of the patients are shown in table 1.

Intervention
Denosumab 60 mg vs placebo administered subcutaneously every 6 months. Patients received daily supplements of least 1 gram of calcium and vitamin D 400 IU. The analysis was by intention to treat.

Outcomes
Primary endpoint: incidence of vertebral fractures and safety and tolerability profile of denosumab.
Secondary endpoints: incidence of non-vertebral and hip fractures.

Results
See table 2.

Authors' conclusion
Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis.

Role of financial sponsors
Financed by the manufacturer of denosumab (AMGEN).

A critical appraisal of the trial
The comparator. Why compare it to placebo?

No one would think of comparing an anaesthetic or antibiotic for pneumonia against placebo, since there are other drugs that have proved effective in these indications. However, after more than 20

Table 1. Baseline characteristics of patients.

VARIABLE		DENOSUMAB (N=3902)	PLACEBO (N=3906)
Age	Mean (years)	72.3±5.2	72.3±5.2
	Age group, n (%)		
	<70 years	1030 (26.4)	1028 (26.3)
	70-74 years	1637 (42.0)	1642 (42.0)
	≥75 years	1235 (31.7)	1236 (31.6)
Body mass index	26.0±4,1	26.0±4.2	
Region, nº (%)	Western Europe	1761 (44.8)	1773 (45.1)
	Eastern Europe	1374 (34.9)	1355 (34.4)
	Latin America	472 (12.0)	462 (11.7)
	North America	282 (7.2)	297 (7.5)
	Australia and New Zealand	44 (1.1)	48 (1.2)
t-score	Lumbar spine	-2.82±0.70	-2.84±0.69
	Total hip	-1.89±0.81	-1.91±0.81
	Femoral neck	-2.15±0.72	-2.17±0.71
Prevalent vertebral fracture, nº (%)	Yes	929 (23.8)	915 (23.4)
	No	2864 (73.4)	2854 (73.1)
	Unreadable or Messing data	109 (2,.8)	137 (3.5)
Serum 25-hydroxyvitamin D (ng/ml)		23.1±11.7	22.9±11.3

Adapted from reference[1].

Table 2. Effect of denosumab on the risk of fracture at 36 months.

OUTCOME	DENOSUMAB n (%)	PLACEBO n (%)	ABSOLUTE DIFFERENCE (CI 95%)	RR or HR (CI 95%)	p VALUE
Primary endpoint					
New vertebral fractures	86 (2.3)	264 (7.2)	4.8 (3.9 to 5.8)	0.32 (0.26 to 0.41)	<0.001
Secondary endpoints					
Nonvertebral fracture	238 (6.5)	293 (8.0)	1.5 (0.3 to 2.7)	0.80 (0.67 to 0.95)	0.01
Hip fracture	26 (0.7)	43 (1.2)	0.3 (-0.1 to 0.7)	0.60 (0.37 to 0.97)	0.04
Other fracture endpoints					
New clinical vertebral fracture	29 (0.8)	92 (2.6)	1.7 (1.1 to 2.3)	0.31 (0.20 to 0.47)	<0.001
Multiple (≥2) new vertebral fractures	23 (0.6)	59 (1.6)	1.0 (0.5 to 1.5)	0.39 (0.24 to 0.63)	<0.001

years of available drugs for the prevention of fractures, the regulatory agencies still maintain the requisite that new drugs be compared to placebo. This means that we do not have any drug which may show acceptable minimum efficacy in the prevention of fractures to be considered as a reference comparator.

Despite the recommendation of regulatory agencies to use placebo as comparator, in the case of denosumab it would have been very interesting to establish a third arm in the FREEDOM trial in order to compare it to bisphosphonates. The interest derives from the fact that bisphosphonates are the most widely employed drugs in the management of osteoporosis and both drugs, by different mechanisms of action, produce the same effects in osteoclasts and osteoblasts. For this reason, it would be fitting to compare them to discover whether there are any differences between denosumab and biphosphonates.

The primary endpoint… is it well defined? Is it clinically relevant?

The primary endpoint is the incidence of morphometric vertebral fractures determined by the semi-quantitative method. Genant and cols[2] defined a fracture as a reduction between 20% and 25% in the height of the vertebra, at any point with respect to the baseline situation. In pivotal studies on alendronate a 20% reduction in height was considered as "fracture"[3,4,5]. In pivotal studies on risedronate, the definition changed arbitrarily to a reduction of 15% of vertebral height[6,7,8]. In the case of denosumab, we do not know what criteria was applied as it was not indicated either in the publication[1], or in the summary of the study protocol[9].

Besides this vague definition of the primary endpoint, we should comment that the clinical relevance of morphometric fractures is questionable.

The FREEDOM trial presents many questionable methodological aspects

The same authors that describe the semi-quantitative method say that "the distinction between borderline deformity (grade 0.5) and definite mild (grade 1) fractures can be difficult and sometimes arbitrary. Another potential deficiency of the semi-quantitative approach is the rather arbitrary distinction between mild (grade 1) and moderate (grade 2) fractures or between moderate and severe fractures (grade 3)".

In the clinical trials in which morphometric vertebral fractures are distinguished from clinical fractures, the latter are usually less than a third. This can also be observed in the FREEDOM trial. For this reason, it is worth questioning the validity of an endpoint in which 70% of the cases are not clinically relevant. In fracture prevention, the primary endpoint of the trials should be the incidence of hip fractures where no doubt exists on its clinical relevance.

The study population. Inclusion and exclusion criteria

The exclusion criteria in the protocol published by the manufacturer do not coincide with those described in the publication. According to the protocol, there were two exclusion criteria: BMD T-score at the hip or the spine of less than 4.0 and subjects with any severe or more than two moderate vertebral fractures on spine X-ray at entry. However, in the publication, a series of other exclusion criteria were added:

Women with diseases affecting the bone metabolism or who had taken oral biphosphonates for more than 3 years. If they had taken biphosphonates for less than 3 years, they were eligible for the trial after 12 months without treatment.

This exclusion criteria leads to uncertainty in identifying efficacy and adverse effects in women who have been under biphosphonates over three years. A considerable proportion of women take bisphosphonates in the long-term. Therefore, there is no data to support the use of denosumab in these women. On the other hand, in women who received biphosphonates for less than 3 years, a washout period of 12 months was established. At no point is this measure justified. Biphosphonates are drugs that accumulate in the bone and their effects last over the years after suspension of treatment.

Women who had received intravenous bisphosphonates, fluoride, or strontium for osteoporosis within the past 5 years.

As before, there is no justification offered for this exclusion. It is understood that women who are under the effects of other bone treatments are to be excluded. However, patients who had received intravenous bisphosphonate therapy more than 5 years ago probably would still be under its effects during the FREEDOM trial because of the above mentioned characteristic of bone accumulation.

Women who received parathyroid hormone or its derivatives, corticosteroids, systemic hormone-replacement therapy, selective estrogen-receptor modulators, or tibolone, calcitonin, or calcitriol within 6 weeks before study enrollment.

Nor is it demonstrated in the case of these drugs that the washout period should ideally last for 6 months.

Results

Eficacy

In the publication of the trial there is no information whatsoever on other medications, comorbidities or health status in both groups. We cannot know whether the groups are balanced.

In the table 2 it can be observed that denosumab reduces morphometric **vertebral fractures** by 4.8% in absolute terms after 3 years of treatment. However, clinical vertebral fractures are reduced by 1.8% only after 3 years under denosumab, which means that 55 women need to be treated for 3 years in order to avoid one symptomatic vertebral fracture.

FDA experts solicited data to investigate vertebral fracture at yearly intervals. In the FDA report, the fracture data was descriptively presented as the number and percentage of vertebral fractures within each 1-year time interval for year 1, year 2, and year 3. In their opinion, the results were "counterintuitive" since one would expect the percentage to either decrease or remain the same but, on the contrary, it inexplicably fluctuated (table 3).

On the other hand, a 0.3% absolute reduction in **hip fracture** risk (secondary endpoint) was observed. The hazard ratio showed a statistically significant lower risk in the denosumab group but the absolute difference did not reach statistical significance. The *hazard ratio* normally magnifies the differences between groups with respect to the absolute difference values. This gives us the idea that the efficacy of denosumab is questionable.

Because of the absolute risk reduction for hip fracture not being statistically significant, the FDA reviewers decided to further investigate hip fracture at yearly intervals. According to the reviewers the results are "counterintuitive." In comparison with the observed incidence of the first year, in the denosumab group there is a reduction in the second year, and an increase in the third year. The percentage within the third year is greater in the denosumab group compared to the placebo group, suggesting that the proportion of hip fractures in the denosumab group has caught up with that in the placebo group. In the placebo group hip fractures were reduced by half in the third year (table 4)[10].

Another point is that no information is provided about what types of fractures were included as "non-vertebral fracture", nor is there information on the incidence of fractures according to their location in each group.

With regard to withdrawals, the published trial indicates that 82% of the patients completed the trial, and 76% received all the injections. No information is given on withdrawals in the different study groups, which is a minimum to be offered in a paper[11]. However, in the EMA's report this information can be found[12].

The trial was carried out in countries in different continents. There is no information on the results according to geographical region. It would be interesting to know whether there were any differences or the data were consistent across the different sites where the trial was carried out.

Safety

The authors affirm that there were no differences between denosumab and placebo in the total incidence of adverse effects, severe adverse reactions, and withdrawals due to adverse reactions. That is the safety profile is similar to placebo. This is very strange and does not coincide with the data available on denosumab from regulatory agencies. The EMA makes a special emphasis on some of the adverse reactions specific to denosumab like hypocalcemia, skin infections, jaw osteonecrosis (just like bisphosphonates), cataracts, and diverticulitis[13]. The FDA published an alert on the the possibility that denosumab increases the risk of severe infections, adverse skin effects, and inhibits bone resorption, giving way to jaw osteonecrosis[14].

The severe irregularities detected in the inspections raise concern about the veracity of the published data

In the description of adverse effects in the FREEDOM trial, it is noteworthy to say that the placebo group presented a statistically significant greater amount of falls and concussions (table 5). The sensation is that study groups were not well balanced.

Another reason of concern about safety results is that the committee of experts evaluated the data without blinding, that is, at every moment they knew what treatment the patients who presented an adverse reaction were receiving. In the publication there was no indication on the composition of the expert committee or on the existence of any potential conflicts of interest.

Duration of the FREEDOM trial

Follow-up of these patients was for 3 years. It is known that bisphosphonates cause important safety problems in the long term (over 3 years). Some of these problems are shared by denosumab, as in the case of jaw osteonecrosis. Thus the reasonable duration for the study should have been longer. Recently, the continuation of the FREEDOM trial was published with results after 5 years of follow-up but unfortunately, after 3 years the placebo arm was discontinued and patients in both groups were given denosumab[15]. For this reason, we do not have valid information on the effects of denosumab in the long term.

Table 3. Number and percentage of new vertebral fractures within each 1-year time interval.

	YEAR 1		YEAR 2		YEAR 3	
	Individuals (n)	Fractures, n (%)	Individuals (n)	Fractures, n (%)	Individuals (n)	Fractures, n (%)
Denosumab	3902	23 (0.59)	3551	17 (0.48)	3323	46 (1.38)
Placebo	3906	49 (1.25)	3503	89 (2.54)	3175	126 (3.97)

Adapted from the FDA[10].

Table 4. Number and percentage of hip fractures within each 1-year time interval.

	YEAR 1		YEAR 2		YEAR 3	
	Individuals (n)	Fractures, n (%)	Individuals (n)	Fractures, n (%)	Individuals (n)	Fractures, n (%)
Denosumab	3902	10 (0.26)	3676	4 (0.12)	3477	12 (0.34)
Placebo	3906	20 (0.51)	3672	14 (0.38)	3430	9 (0.26)

Adapted from the FDA[10].

Risk of bias

In clinical trials, there are some aspects of design, development and data reporting that may increase the risk of bias with regard to the results and conclusions. This risk analysis orients us toward the credibility of the study. The Cochrane collaboration has developed a tool to determine the risk of bias in clinical trials[16]. In the publication of the FREEDOM trial there is no information on the sequence generation or allocation concealment and data on withdrawals are incomplete. However in the EMA's report some information regarding these issues is available. Perhaps, one of the key aspects in the quality of this study is that blinding was inadequate, as there is acknowledgement of the open **(not blinded)** monitoring of the safety data every 6 months.

On the other hand, the trial does not offer sufficient information to ensure that the patients in both groups were well balanced. There is no information on concomitant medication or on comorbidities of the subjects under study.

Protocol violations and data manipulation in the FREEDOM trial

According to the EMA's report[12], the FREEDOM trial has been subjected to at least 3 inspections (pages 19, 20, 24 and 25). One of them was carried out by the authorities in Lithuania in one of the centres participating in this trial. The irregularities observed were of such calibre that it was decided to withdraw all patients from this centre in the trial.

The EMA ordered more inspections in other participating centres of and the CRO (*Contractual Research Organization*) which was subcontracted to implement the trial and perform the assessments of X-rays and DXA-scans. In the centres evaluated, severe protocol violations were discovered. Among them, fracture status could be changed from "incident" to "prevalent" without adjudication of the X-ray investigation. In fact, fracture status was changed by a late reader for 288 trial subjects, and fracture status at screening was changed for more than 75% of these subjects. Inexplicably, the patients from these two centres were not excluded for the analysis.

With respect to the CRO inspections, serious irregularities were observed that had already been detected in a previous inspection and it was confirmed that insufficient corrective or preventive actions had been implemented. The EMA recommends that a follow-up inspection on the CRO should be performed. Surprisingly, the report concludes that "the re-inspection will not be a part of the Prolia (denosumab) application."

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Table 5. Adverse events.

EVENTS	DENOSUMAB (N=3886)	PLACEBO (N=3876)	P
All	3605 (92.8)	3607 (93.1)	0.91
Serious	1004 (25.8)	972 (25.1)	0.61
Fatal	70 (1.8)	90 (2.3)	0.08
Leading to study discontinuation	93 (2.4)	81 (2.1)	0.39
Leading to discontinuation of a study drug	192 (4.9)	202 (5.2)	0.55
Adverse events:			
Infection	2055 (52.9)	2108 (54.4)	0.17
Cancer	187 (4.8)	166 (4.3)	0.31
Hypocalcemia	0	3 (0.1)	0.08
Osteonecrosis of the jaw	0	0	n.a.
Serious adverse events:			
Cancer	144 (3.7)	125 (3.2)	0.28
Infection	159 (4.1)	133 (3.4)	0.14
Cardiovascular event	186 (4.8)	178 (4.6)	0.74
Stroke	56 (1.4)	54 (1.4)	0.89
Coronary heart disease	47 (1.2)	39 (1.0)	0.41
Peripheral vascular disease	31 (0.8)	30 (0.8)	0.93
Atrial fibrillation	29 (0.7)	29 (0.7)	0.98
Adverse events occurring in at least 2% of subjects:			
Eczema	118 (3.0)	65 (1.7)	<0.001
Falling	175 (4.5)	219 (5.7)	0.02
Flatulence	84 (2.2)	53 (1.4)	0.008
Serious adverse events occurring in at least 0.1% of subjects:			
Celullitis (including erysipelas)	12 (0.3)	1 (<0.1)	0.002
Concussion	1 (<0.1)	11 (0.3)	0.004

Conclusions

Denosumab has shown efficacy compared to placebo in the reduction of morphometric vertebral fractures, an endpoint of dubious clinical relevance.

Data on prevention of hip fractures are inconclusive.

Safety data published do not concur with the drug information available from regulatory agencies. There is no information on long-term safety.

There are no comparative data with bisphosphonates.

Due to the exclusion criteria in the trial, the results are not applicable to women previously treated with bisphosphonates.

Given the high risk of bias of the FREEDOM trial, the conclusions derived from this study should be considered with precaution. Furthermore, the serious irregularities found in the trial inspections raise concern on the veracity of the published data.

References

1. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361(8):756-65.

2. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bobe Miner Res 1993;8:1137-48.

3. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC et al. Randomised trial of effect of alendronate on risk fracture in women with existing vertebral fractures. Lancet 1996;348:1535-41.

4. Cummings SR, Black DM, Thompson D, Applegate WB, Barret-Connor E, Musliner T, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. Results from the fracture intervention trial. JAMA 1998;280:2077-82.

5. Liberman UA, Weiss SR, Broll J, Minne HW, Hui Q, Bell N et al. Effects of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995;333: 1437-43.

6. Reginster JY, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML et al. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Osteoporos Int 2000;11:83-91.

7. Harris ST, Watts NB, Genent HK, McKeever CD, Hangartner T, Keller M et al. Effects of risedronate treatment on vertebral and non vertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. JAMA 1999;282:1344-52.

8. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C et al. Effect of risedronate on the risk of hip fracture in elderly women. N Engl J Med 2001;344:333-40.

9. A study to Evaluate Denosumab in the Treatment of Postmenopausal Osteoporosis (NCT00089791). Disponible en http://www.clinicaltrials.gov/ct2/show/NCT00089791?term=NCT00089791&rank=1 (accedido el 13/02/2012)

10. U.S. Food and Drug Administration, June 1, 2010. NDA 125320. Prolia (denosumab) Injections. Statistical Review(s). CDER, FDA.

11. David Moher, Kenneth F Schulz and Douglas G Altman. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. *BMC Medical Research Methodology* 2001, **1**:2

12. European Medicines Agency, 2010. EMEA/H/C/001120. Prolia (denosumab). European Public Assessment Report, Scientific Discussion. EMEA.

13. Ficha técnica de Prolia®. Disponible en: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001120/WC500093526.pdf (accedido el 14/02/2012).

14. U.S. Food and Drug Administration, September, 2011. BL 125320. Prolia (denosumab) Injections. Risk Evaluation and Mitigation Strategy (REMS) CDER, FDA.

15. Papapoulus S, Chapurlat R, Libanati C, Brando ML, Brown JP, Czerwinski, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. JBMR 2012;27(3):694-701

16. Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

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