Neyro Bilbao JL[1], Palacios Gil-Antuñano S[2], Cano Sánchez A[3]
1 Servicio de Obstetricia y Ginecología - Hospital Universitario de Cruces - Universidad del País Vasco - UPV-EHU - Baracaldo - Bizkaia
Grupo de trabajo en Osteoporosis de la Asociación Española para el Estudio de la Menopausia (AEEM)
2 Instituto Palacios de Investigación y Salud de la Mujer - Madrid
3 Servicio de Obstetricia y Ginecología - Hospital Universitario Dr. Peset - Universidad de Valencia
Grupo de trabajo en Osteoporosis de la Asociación Española para el Estudio de la Menopausia (AEEM)

Profile of action of denosumab in treatment of osteoporosis

Correspondence: José Luis Neyro Bilbao - Gran Vía, 81, 4º - 48011 Bilbao (Spain)
e-mail: doctor@neyro.com

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Summary
The recent discovery of the RANK/RANKL/OPG system (RANK: Receptor Activator for Nuclear Factor B; RANKL: Receptor Activator for Nuclear Factor B Ligand; OPG: osteoprotegerin) as final effector in osteoporosis pathogenesis have lead to the development of new therapeutic strategies. Denosumab is a human monoclonal antibody that, like OPG, binds to RANKL preventing RANK activation, thus decreasing bone turnover and increasing bone mineral density. Denosumab is administered subcutaneously every 6 months. Clinical trials have demonstrated efficacy on bone mineral density and reduction of fractures in postmenopausal women and a favourable safety profile.

Key words: *postmenopausal osteoporosis, osteoprotegerin, RANKL, denosumab.*

Clinical case

A 60 year old woman who attended a clinic for a general preventative check, with an evaluation of possible osteoporosis. Personal history: multiple birth (3 children) with menopause at 51 years of age. Did not have climeratic syndrome, which meant that she did not require hormonal treatment. Moderate smoker of 15 cigarettes/day and occasional drinker. With sedentary job in office administration. Generally healthy, at 52 years of age after a fall in her doorway she had a right Colles fracture without complications. Family history: hip fracture in her mother at 78 years of age. Physical examination: weight, 60.6 kg; height, 159 cm (BMI 24). Complementary examinations: bone densitometry showed a T-score of -2.4 in the lumbar spine and -1.9 in the hip. According to the FRAX tool, the probability of major osteoporotic fracture after 10 years is 10%, and 2% for a hip fracture. Given these characteristics of the patient and her personal and family histories, and taking into account the risk of fracture at 10 years according o the FRAX index, it is considered recommendable that she adopt some hygiene measures, such as stopping smoking, taking exercise and control of weight, with the aim of not going below the ideal weight. In terms of pharmacological measures the administration of an antiresorptive drug such as denosumab is also contemplated, along with calcium and vitamin D supplements.

Introduction

The clinical case shows the importance of investigating the situation of bone mass in an apparently healthy, recently menopausal patient, during a normal health check. Her history of bone fracture and her risk factors suggest the presence of low bone mass, as the bone densitometry demonstrated.

Taking into account the impact of osteoporosis (OP) on the quality of life of patients and its general repercussions on society, we have considered it to be of interest to carry out this review concerning the monoclonal antibody denosumab, an antiresorptive drug recently developed following the discovery of the final effector in osteoporosis, the RANK/RANKL/OPG system[1].

Pharmacological action on the RANK/RANKL/OPG system. Denosumab

The pharmacological treatment of OP includes antiresorptive drugs such as the biphosphonates, raloxifene (and other selective estrogen receptor modulators - SERMs – such as bazedoxifene) and calcitonin; anabolic drugs such as teriparatide or whole molecule recombinant PTH; and dual action drugs such as strontium ranelate[2]. All these have been trialled during their clinical development with a range of doses of calcium and vitamin D as pharmacological supplements. From the knowledge of the RANK/RANKL/OPG system different ways of regulating the condition have been proposed[3,4]:

In relation to RANKL

- Inhibition of its expression: by means of 17ß-estradiol.

- Blocking RANKL: by means of OPG or OPG-like proteins, the application of neutralising proteins or anti-RANKL antibodies or generation of antibodies by autovaccination.

In relation to RANK

- By the interruption of its bond with RANKL or by the suppression of the postreceptor signal (by 17ß-estradiol).

In relation to OPG

- By increasing its endogenous production (by 17ß-estradiol, raloxifene, biphosphonates...), by transgenic overexpression of OPG or by the administration of OPG or OPG-like proteins.

Within this line of development is found denosumab (AMG 162) (DMAB), an anti-RANKL monoclonal antibody which prevents RANKL's action by impeding its coupling with its receptor RANK. In the development of the monoclonal antibodies, the first were 100% murine in origin, but given the problems this caused, antibodies have increasingly been developed with higher human content until they are completely human (100%), with more appropriate pharmacokinetic characteristics and better immunogenicity[5]. DMAB belongs to this last group and its clinical development began in 2000. It consists of an isotope of entirely human immunoglobulin IgG_2, with a high affinity with, and specificity for, RANKL[6] and which acts in a similar way to OPG, in that it prevents the interaction between RANKL and RANK and reduces the differentiation, activity and survival of the osteoclasts, thereby inhibiting bone resorption. One of the potential risks of the use of OPG molecules is the generation of antibodies which may react with the endogenous OPG. However, no anti-DMAB[7,8] neutralising antibodies have been observed, probably due to the structure of DMAB not being similar to that of OPG.

• Pharmacokinetics and pharmacodynamics of DMAB (Preclinical and phase I studies)

Although the pharmacokinetic properties of DMAB are not totally defined, considering the pharmacokinetic properties of the monoclonal antibodies, its saturable bond with the corresponding antigen would take a non-linear distribution and elimination[9]. In addition, based on studies with similar IgG antibodies, DMAB is probably absorbed by the lymph system and later drained into the vascular system[6]. Its bioavailability would be between 50 and 100% with a similar distribution to the plasmatic volume and clearly dependent on the reticulo-endothelial system[6]. A study of a single dose compared with a placebo showed the non-linear pharmacokinetics of DMAB[8], with a) a prolonged absorption which provided some maximum blood concentrations which increased disproportionately (2.6 times) in relation to the increase in dose, and which were observed 5-21 days after their administration; b) a prolonged half-life of up to 32 days; and c) and an average residence time in the blood of 12 to 46 days depending on the dose. At the recommended dose of 60 mg subcutaneously (see below), the time to maximum concentration is 26 days[10].

The action of DMAB is rapid, prolonged and reversible. The long duration of its effect may be attributed to its half-life and its osteoclast inhibitor effect. Preclinical models suggest that the delay in the recuperation of the osteoclasts after the suspension of the inhibition of RANKL appears to be due to the time needed for their regeneration from the precursor cells[11]. However, once the drug has been eliminated and the osteoclasts have been regenerated, its antiresorptive effect rapidly disappears. This reversibility distinguishes DMAB from the biphosphonates since, differently from them, it is not incorporated into the bone matrix[12]. As has been shown by the changes in markers for bone remodelling (amino-terminal telopeptide of type I collagen (NTx) in urine, and carboxy-terminal telopeptide of type I collagen in blood, among others), the subcutaneous administration of DMAB reduces the function of the osteoclasts, quickly (in between 12 and 72 hours) and sustainably (up to 6 months), as well as being reversible, as is shown by the increase in the aforementioned markers when the drug disappears from circulation, and recoverable when the therapy is reinstated

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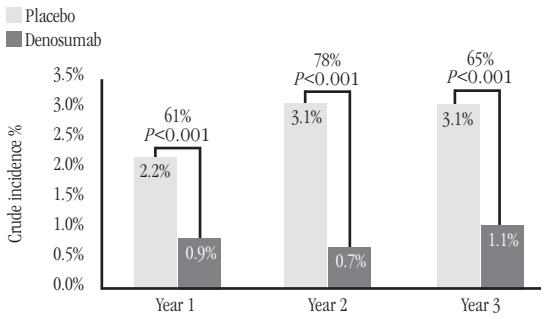
• Clinical efficacy of DMAB (Phase II and III clinical trials)

The efficacy and safety of DMAB was initially evaluated in the phase II study, a randomised, double blind, dose-ranging study, in which 412 postmenopausal women with osteoporosis received DMAB subcutaneously over 12 months, every three months (at doses of 6, 12, or 30 mg), or every 6 months (at doses of 14, 60, 100 or 210 mg), the treatment masked with weekly alendronate (at a dose of 70 mg) or placebo[7]. Treatment with DMAB was associated with a rapid increase in bone mineral density in the spine, hip and distal third of the radius which was higher than that observed with the placebo, and similar, even higher (in the hip and distal extreme of the radius) than that found with 70 mg of alendronate weekly[7]. From this study, the doses considered to be optimum were 30 mg/3 months and 60 mg/6 months, the latter being chosen for subsequent development[7]. The efficacy of DMAB has subsequently been confirmed in 4 phase III studies in women with osteopenia or OP. In a clinical trial with randomisation stratified as a function of the duration of the menopause (>5 years or ≤5 years), double blind, of two years' duration, carried out in 332 postmenopausal women with low BMD (T-score in lumbar spine – LS – of between -1.0 and -2.5), the efficacy of 60 mg subcutaneous DMAB every 6 months was compared with that of a placebo[14]. The DMAB increased significantly the BMD in the LS at 2 years in comparison with the placebo (6.5% vs. -0.6%, p< 0.0001), which was independent of the time passed since the menopause[14].

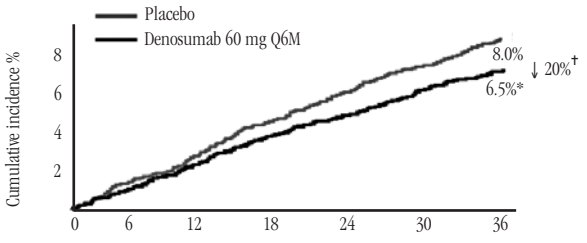
Figure 1. Time until the first fracture with DMAB as opposed to the placebo (Adapted from Cummings and cols.)

Figure 1A. The effect of denosumab on new vertebral fractures year on year
Phase III: FREEDOM study



Intention to treat, last observation carried out in the following analysis.
The percentage of new fractures is calculated using the number of patients with a radiological evaluation of the spine at the baseline and at least one other in the post-baseline period.
Adapted from: Cummings SR et al. N Engl J Med 2009;361:756-65

Figure 1B. Effect of denosumab on the time until the first non-vertebral fracture during 36 months.
Phase III: FREEDOM study

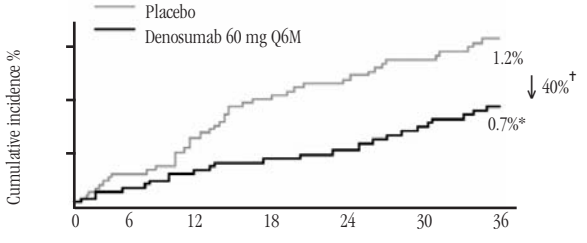


Number of patients at risk

Placebo, n	3.906	3.750	3.578	3.410	3.264	3.121	3.009
Denosumab, n	3.902	3.579	3.594	3.453	3.337	3.228	3.130

† Non-vertebral fractures were reduced by 20% (95% CI: 0.67, 0.95)
* *P*= 0.01
Adapted from: Cummings SR, *et al.* N Engl J Med 2009;361:756-65

Figure 1C. Effect of denosumab on the time until the first hip fracture during 36 months
Phase III: FREEDOM study



Number of patients at risk

Placebo, n	3.906	3.799	3.672	3.538	3.430	3.311	3.221
Denosumab, n	3.902	3.796	3.676	3.566	3.477	3.397	3.311

† Hip fractures were reduced by 40% (95% CI: 0.37, 0.97)
* *P*= 0.04
Adapted from: Cummings SR, *et al.* N Engl J Med 2009;361:756-65

Another randomised, double blind with double simulation trial carried out in 1,189 postmenopausal women with a T-score of -2.0 or less in the spinal column or total hip, compared the efficacy of DMAB at the same dose with that of alendronate of 70 mg weekly[15]. In this study, after a year of treatment, DMAB was higher than alendronate in the increase of BMD in total hip (3.5% vs. 2.6%, p< 0.0001) and in the other locations in the bone, with both drugs showing a similar safety profile. This apparent superiority of DMAB over alendronate in the increase in BMD has also been demonstrated in another clinical trial, double blind with double simulation, in which 504 postmenopausal women with a T-score in LS or total hip between -2.0 and -4.0, who had received 70 mg of alendronate weekly, orally, over one month, were randomly chosen to continue with weekly alendronate or to change to DMAB at a standard dose for one year[16]. One of the inclusion criteria in this study was whether the patient had been in treatment with weekly alendronate for at least 9 months continuously. The women who changed to DMAB experienced an increase in BMD in the total hip a year after treatment of 1.9% compared with 1.05% observed in the group which received alendronate (p<0.0001); the increases in BMD were also significantly higher with DMAB in the LS, femoral neck (FN) and distal third of the radius, with both drugs having a similar safety profile[16].

In a survey carried out in all the women patients from these last two trials it was found that those treated with DMAB administered subcutaneously preferred this treatment, were more satisfied with it, and that it bothered them less than the weekly oral treatment with alendronate[17].

Finally, within what has been the clinical development of DMAB in the treatment of OP it is worth noting a recently published randomised placebo controlled clinical trial, the FREEDOM study[18]. In this trial were included 7,868 women from 60 to 90 years of age with a T-score below -2.5 but not less than -4.0 to whom was administered DMAB at a dose of 60 mg every 6 months over 3 years. In comparison with the placebo, DMAB significantly reduced the risk of vertebral fractures (reduction of relative risk (RRR) of 68%) in any of the 3 years considered, even when separating (Figure 1A) non-vertebral (RRR, 20%) (Figure 1B), and hip fractures (RRR,40%) (Figure 1C).

In addition, treatment with DMAB was associated with a relative increase in mineral density in the LS and hip, as well as a reduction in markers for bone formation (PINP, amino-terminal propeptide of type 1 procollagen) as well as those for resorption (CTX), significantly in comparison with the placebo[18], already from the first month and during the whole time the trial lasted. The authors concluded that DMAB, due to its action as an inhibitor of RANKL, reduces bone resorption and increases bone mineral density, which means that it offers a valid alternative in the treatment of OP[18].

• Clinical safety

Due to the interference of DMAB with the RANK/RANKL/OPG system, and taking into account the fact that RANKL is expressed both in bone cells and in immune cells[19], the possible incidence of infections or neoplasms with this drug merits special attention. However, in the clinical studies published to date no significant differences have been observed between DMAB, the placebo and alendronate in relation to the notification of serious adverse effects, either in terms of infections or neoplasms. Only in one study were 6 infections which required hospitalisation reported in the DMAB group during its extension phase to 24 months[20]. However, all these corresponded to infections acquired in the community, did not follow a specific common pattern of infection and responded adequately to standard antibiotic treatment[20].

The aforementioned FREEDOM study[18] did not observe any increase in the risk of cancer, infections, cardiovascular disease, delay in the consolidation of factures or hypocalcemia, nor were any cases of osteonecrosis of the jaw reported after 36 months following the use of DMAB. The adverse events most frequent or relevant to the FREEDOM study are presented in Table 1. Similar, coherent, results regarding safety have been reported in another randomised double blind clinical trial in 1,468 patients with prostate cancer subject to androgenic deprivation and treated with DMAB or a placebo for 36 months[21]. However, in the FREEDOM study the female patients treated with DMAB, in comparison with those treated with the placebo had a significantly higher frequency of eczema, flatulence and cellulitis as serious adverse effect (Table 1)[18]. While on the contrary, in comparison with the placebo, those treated with DMAB had a significantly lower incidence of falls[18], a circumstance which, without doubt, would merit a much deeper analysis due to its possible implications in the near future.

In the other three phase III trials[14,15,16], the global incidents of adverse events, and of serious adverse events, was similar between the two treatment groups studied. In the phase II clinical trial, in which were included an arm given treatment masked with alendronate, with the exception of one significantly higher incidence of dyspepsia with alendronate no differences were observed in the profile of adverse events between the patients who received denosumab and those who received the placebo or alendronate[7]. However, in another phase III comparison with alendronate no differences were found in the frequency of adverse events between DMAB and alendronate, including gastrointestinal disorders[15]. Similarly, in the clinical trial substituting alendronate by DMAB, there were no differences in the profile or frequency of adverse events between patients who changed to DMAB and those who continued with alendronate, the most frequent adverse events being nasopharyngitis (13.4% vs 10.8%), back pain (10.7% vs 11.6%), bronchitis (6.3% vs 5.6%), arthralgia (5.9% vs 10.4%) and constipation (5.1% vs 4.8%)[16].

Table 1. Adverse events with denosumab in the FREEDOM study (adapted from Cummings and cols.[18])

	Placebo (n=3.876)	Denosumab 60 mg Q6M (n=3.886)	*p*-value
Adverse events			
Infection	2,108 (54.4)	2,055 (52.9)	NS
Tumoral process	166 (4.3)	187 (4.8)	NS
Reaction at site of injection	26 (0.7)	33 (0.8)	NS
Symptomatic hypocalcemia	3 (0.1)	0 (0)	NS
Delayed recuperation of fracture	4 (0.1)	2 (0.05)	NS
Fracture of femoral diaphysis	3 (0.1)	0 (0)	NS
Fracture or humerus (not at the site of the joint)	1 (0.03)	0 (0)	NS
Osteonecrosis of the jaw	0 (0)	0 (0)	NS
Adverse events with an incidence of ≥ 2% and $p \leq 0.05$ in comparison with the placebo			
Eczema	65 (1.7)	118 (3.0)	<0.001
Falls*	219 (5.7)	175 (4.5)	0.02
Flatulence	53 (1.4)	84 (2.2)	0.008
Serious adverse events			
Tumoral process	125 (3.2)	144 (3.7)	NS
Infection	133 (3.4)	159 (4.1)	NS
Cardiovascular events	178 (4.6)	186 (4.8)	NS
Heart attack	54 (1.4)	56 (1.4)	NS
Coronary disease	39 (1.0)	47 (1.2)	NS
Peripheral vascular disease	30 (0.8)	31 (0.8)	NS
Auricular fibrillation	29 (0.7)	29 (0.7)	NS
Serious adverse events with an incidence ≥ 0.1% and $p \leq 0.01$ in the comparison with the placebo			
Cellulitis (including erysipelas)	1 (<0.1)	12 (0.3)	0.002
Commotion	11 (0.3)	1 (<0.1)	0.004

* Excludes falls happen on the day of the fracture

Finally, in one of the comparative clinical trials with placebo the patients who received DMAB had a significantly higher incidence of constipation (11% vs 4.8%), sore throat (9.1% vs 3%) and exanthema (8.5% vs 3%)[14]. These circumstances, apparently, to not have major clinical implications, although it is necessary to indicate them.

Final comments

Pharmacological research in the field of biological therapies has recently designed the first entirely human monoclonal antibody against RANK-L which has a unique physiological action mechanism which acts at the physiopathological roots of the disease. It may be said to be an "alternative pharmacological variant of osteoprotegerin", which, by bonding specifically to RANK-L impedes OP's accelerated bone destruction.

DMAB has shown in many well designed clinical trials (randomised, placebo-controlled, prospective, multicentred) notable increases in BMD in all locations measured and in the main types of

bone, cortical and trabecular, always higher than that observed in the placebo arm. The same applies, when DMAB is compared with an arm with active treatment with alendronate.

In addition, in a major phase III trial, the confirmation of the notable protection against fractures in all locations (with no distinction between vertebral, hip and non-vertebral), positions it as the first choice drug in the well-stocked therapeutic arsenal against OP.

The demonstrated reversibility of its effects on the bone once the administration of the drug is withdrawn, as well as its good general pharmacological safety profile is comparable to the placebo and to alendronate, the latter being a paradigm in the classic pharmacopeia against osteoporosis , especially as a function, nowadays, of its accumulated experience of over 13 years. DMAB's easily delivered dosage, administered subcutaneously twice a year makes it, in theory, a good candidate to address the chronic pathology that OP presents.

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