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Consensus Paper

Spanish Menopause Society position statement: Use of denosumab in postmenopausal women

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ABSTRACT

Denosumab is a new drug developed for the treatment of osteoporosis. Moreover, increasing evidences link denosumab with benefits in cancer, an area of interest for those in charge of the postmenopausal health. Denosumab has shown efficacy in the control of bone loss associated with hypogonadic states created by chemotherapy in breast and other cancers. Moreover, some studies reveal efficacy in reducing the progression of metastases. A panel of experts from the Spanish Menopause Society has met to develop usage recommendations based on the best available evidence.

1. Introduction

Denosumab (Dmab) is a new drug developed for the treatment of postmenopausal osteoporosis (PMOP). Dmab has added to the therapeutic arsenal of clinicians who take care of chronic diseases associated with aging, like for example gynaecologists attending postmenopausal women, or others. Moreover, the increasing evidences on the impact of Dmab in fields exceeding the care of osteoporosis, like the hypogonadic states created by chemotherapy in breast and other cancers, adds interest for those in charge of the postmenopausal health. Recently, the Spanish Menopause Society issued a clinical practice guideline regarding the treatment of PMOP, where a sequential strategy was proposed in order to tailor the anti-osteoporotic treatment to the specific needs of women at the different postmenopausal stages [1,2]. This all adds to existing debates in PMOP management, like those related with the comparative efficacy of generic formulas and new alternatives, as well as the long term safety of anti-resorptive treatments.

Because Dmab has been demonstrated to be effective and safe in the treatment of PMOP, a panel of experts from the Spanish Menopause Society met to establish a set of recommendations for the use of Dmab in patients with PMOP based on the best available evidence. The use of the antibody in other clinical conditions, such as breast cancer, was also analysed. The Spanish Menopause Society considers it appropriate to develop its own recommendations based on the GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) system to clarify clinical practice guidelines and to classify the quality of the evidence and the strength of the recommendations [3].

2. Mechanism of action

The discovery that different cytokines are potent regulators of the differentiation of osteoclasts, the bone cells responsible for bone resorption, has widened the spectrum of potential agents for controlling bone loss. The role of the receptor activator of nuclear factor kappa-B ligand (RANKL) in that process is crucial [4]. Osteoprotegerin (OPG) is a glycoprotein produced by osteoblasts and by B-lineage lymphocytes in bone marrow [5]. OPG acts as a decoy

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Table 1
Summary of results with Dmab.

Effect on BMD and bone turnover markers (BTM)
Marked reduction of BTM and increased BMD at the spine, total hip, one-third radius and total body ($p < 0.0001$ vs placebo) [8–12].
Higher anti-resorptive power than bisphosphonates. The advantage of Dmab was observed at both the hip and the spine when compared with alendronate [8,9,13]. Greater BMD gains and lower BTM were also observed in comparison with other bisphosphonates, like ibandronate or risedronate at the same territories ($p < 0.001$ at all sites) [14,15].
Effect on fracture risk
The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study showed that the cumulative incidence of new vertebral fractures was 2.3% in the Dmab group and 7.2% in the placebo group (risk ratio, 0.32; 95% confidence interval [CI], 0.26 to 0.41; $p < 0.001$). There was also a protective effect of Dmab for nonvertebral fractures and hip fractures, which exhibited a relative decrease of 20% ($p = 0.01$) and 40% ($p = 0.04$), respectively [16].
The extended FREEDOM study confirmed that BMD continued increasing in the long-term group during the 6-year period, and fracture incidences remained low [17,18].
Dmab achieved a 40% relative risk reduction in wrist fracture when selecting women with a femoral T-score equal to or lower than −2.5 ($p = 0.03$)[19].

receptor for RANKL. The OPG/RANKL binding therefore prevents the activation of RANK by RANKL and limits osteoclastogenesis [6].

Dmab is a human monoclonal antibody (IgG2) that binds to RANKL with high affinity. The subsequent blockade of the RANKL/RANK interaction mimics that of OPG and impairs osteoclastogenesis. A drastic reduction of bone resorption at both the trabecular and the cortical bone follows [7].

3. Use of Denosumab in postmenopausal osteoporosis

Table 1 summarises the impact of Dmab as confirmed in different controlled clinical trials.

Despite the advantages of Dmab against bisphosphonates in bone turnover markers (BTM) and bone mineral density (BMD), the absence of face-to-face studies exploring the impact on fractures limits the establishment of preferences between approved anti-resorptives in clinical practice.

A recent meta-analysis has positioned Dmab at a level similar to teriparatide and bisphosphonates with regard to risk reduction for fractures and superior to bazedoxifene, raloxifene and strontium ranelate [20]. The decision about which anti-resorptive to use must be, in any case, tailored to the profile and the preferences of the user.

4. Safety

As a result of the specific mechanism of action of Dmab, safety may be affected in two ways. First, there is the strength of Dmab as an anti-resorptive, which may translate into an increase in adverse events of processes related to an insufficient regeneration of bone. Osteonecrosis of the jaw (ONJ) or atypical fractures emerge as potential threats in this regard. Second, there is the interference of Dmab with pathways where RANKL is a significant mediator, particularly in the immunological system. Increased susceptibility to infections or to malignancies is a possible result.

Data from the six-year extension of the Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) study has confirmed six cases of ONJ and one case of an atypical femoral fracture [18]. Another area of concern, also in relation to the role of Dmab as a potent anti-resorptive, is in possible delays to the healing of fractures. This observation has been communicated in a press release to health professionals by Amgen, the manufacturer of Dmab [21].

Consistent with its high anti-resorptive potential, Dmab may increase pre-existing hypocalcaemia. Consequently, supplementation with calcium and vitamin D is recommended prior to Dmab administration, particularly in women with severe renal impairment.

The interference of Dmab with RANKL in pathways other than those of bone metabolism has also received attention. Increased rates of infections and tumours subsequent to potential deficiencies in the immunological system have been investigated. The overall incidence of infections were similar between Dmab and placebo in the FREEDOM study, but serious infections leading to hospitalisation, including erysipelas, cellulitis, and infections involving the gastrointestinal system, renal and urinary systems, ear, and endocarditis were numerically higher in the Dmab group compared with placebo [22]. However, the number of events was small and no relationship was observed between serious adverse events of infections and the timing of administration or duration of exposure to Dmab. Consistent with that finding, the six-year extension of the FREEDOM study found that the incidence rate of adverse events, including infections, did not increase over time [18].

Eczema and flatulence were reported more frequently in the group treated with Dmab in the FREEDOM trial [16].

Worries about an increased susceptibility to cancer with Dmab stem from observations of binding of OPG to the tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL), which is a protein that induces cellular apoptosis. Given the similarities between Dmab and OPG, the question has arisen of whether Dmab might favour tumourigenesis. Nonetheless, the published data have not reported significant differences or a trend of higher tumour risk in subjects treated with Dmab.

5. Preference and satisfaction

Participants in the Determining Efficacy: Comparison of Initiating Denosumab versus AlEndronate (DECIDE) and Study of Transitioning from AleNdronate to Denosumab (STAND) studies were questioned about their treatment preferences and satisfaction using the Preference and Satisfaction Questionnaire (PSQ). The PSQ is a 34-item questionnaire that was developed specifically to assess patient preference and satisfaction with a Q6 M injection versus weekly tablet for the treatment of low bone mass. Significantly more patients preferred and were more satisfied with the 6-month injection versus the weekly tablet ($p < 0.001$) [23]. Another study assessed perceptions of subcutaneous Dmab or oral alendronate and how these perceptions influence adherence. For that, 250 postmenopausal women with low bone mass were randomised to Dmab Q6 M for one year followed by alendronate 70 mg weekly, or vice versa. Participants preferred Dmab to alendronate and had more positive perceptions of Dmab than alendronate. These perceptions were associated with better adherence [24].

6. Practical recommendations about the use of denosumab

6.1. Dose and assessment

Dmab is administered in the form of 60 mg subcutaneous injections at 6-month intervals for the treatment of osteoporosis. The use of Dmab does not require specific measures prior to treatment or for monitoring of patients. The concomitant use of calcium and vitamin D supplements is recommended, particularly in patients with hypocalcaemia. Monitoring of women treated with Dmab does not require different specific measures than other anti-resorptive drugs.

6.2. Use in renal disease

When not eliminated via urine, there are no restrictions on the use of Dmab in patients with any degree of renal insufficiency, except hypocalcaemia, in which case careful monitoring of serum calcium levels is required [25].

6.3. Treatment discontinuation

The initial Phase 2 trial included two arms in which Dmab was interrupted after 24 months of therapy. Participants in one of the arms were subjected to retreatment for 12 additional months after a 12-month suspension [9]. Alendronate was also discontinued. Women whose Dmab treatments were interrupted for 12 months experienced a decrease in BMD that mirrored the observed increase during the previous one-year treatment period. Retreatment with Dmab for an additional 12 months increased BMD in a magnitude similar to what had been gained initially. BTM after Dmab interruption rapidly increased to a level similar to the pretreatment level, and decreased subsequently with retreatment. The BMD of women after interrupting alendronate slowly decreased, as reported in previous studies with bisphosphonate. It seems, therefore, that Dmab has an on/off effect on bone metabolism that switches more quickly than bisphosphonates. Nevertheless, these data refer only to BMD changes and the translation in terms of fracture risk is unknown.

7. Denosumab in patients with cancer

7.1. Prevention of bone impact of hypogonadism

Women with malignancies often receive treatments that involve severe hypogonadism. The preservation of bone health has prompted the development of protocols with anti-resorptives in which bisphosphonates have occupied a central role. The high anti-resorptive power of Dmab has raised interest in its use as an alternative [26].

The impact of Dmab on the bone mass of osteopaenic women with breast cancer who were receiving treatment with aromatase inhibitors was studied in 252 women randomised to either Dmab or a placebo for 24 months. Dmab increased BMD at all assessed sites, including the distal third of the radius [27]. The magnitude of the impact was similar to what has been shown for zoledronic acid, an intravenously administered bisphosphonate.

HALT-BC was only designed to investigate the impact of Dmab on bone mass, but the positive results raised questions about anti-fracture protection. There is now an on-going phase III trial, ABCSG-18, which investigates whether Dmab will reduce the rate of first clinical fractures in women with non-metastatic breast cancer receiving aromatase inhibitor therapy [28].

7.2. Progression of cancer

Two closely related areas have captured the interest of investigators in relation to Dmab. One relates to the reduction of skeletal related effects (SRE) resulting from established bone metastases in the context of advanced breast cancer, as already shown for bisphosphonates. The other area of interest derives from data obtained in preclinical studies, which suggest that the inhibition of RANKL by Dmab might translate into an impact on tumourigenesis and in the control of disease progression [29].

A face-to-face randomised study of 2046 women with breast cancer and bone metastases showed that Dmab was superior to zoledronic acid in preventing or delaying SREs [30]. Overall survival, disease-free survival and adverse events were similar with both treatments. Advantages to Dmab versus zoledronic acid were also found in men with castration-resistant prostate cancer [31] and in patients suffering from other forms of advanced cancer [32].

The potential interference of Dmab with the progression of cancer is under scrutiny. The D-CARE study investigates whether Dmab may prevent disease recurrence in the bone or in any other part of the body when it is given as adjuvant therapy for women with early stage breast cancer who are at high risk of disease recurrence [33].

8. Cost-effectiveness analysis

8.1. In osteoporosis

The improved adherence suggested in comparative studies favours Dmab, which would achieve a higher impact in the number of fractures avoided. Therefore, Dmab would be a cost-effective alternative, particularly in patients with a high risk of fractures and a low expected compliance with oral treatments. This consideration is at the base of the recommendations of the National Institute for Health and Clinical Excellence (NICE) in the UK, which limits the use of Dmab to post-menopausal women at increased risk of fracture who cannot comply with the special instructions for administering oral bisphosphonates (BPs), or who have an intolerance of, or contraindication to, those treatments [34]. Similarly, medico-economic analyses in Sweden, Canada and the UK concluded that Dmab may be cost-effective for women with a high risk of fractures and for women who are intolerant and/or contraindicated to oral BPs [35,36].

However, other studies have initiated a trend towards less restrictive cost-effective analyses for Dmab. For example, Belgian investigators have positioned Dmab as a more cost-effective strategy than oral BPs, including generic alendronate, for osteoporotic women ≥60 years old [37]. A systematic review from the same group came to the same conclusion after reviewing the available evidence published up to April 2012 [38]. Two studies, including one of an American group, have concluded that Dmab dominates bisphosphonate options, even generic alendronate, in US postmenopausal women and in Swedish older (≥75 years old) osteoporotic men [39,40].

To summarise, there is heterogeneity in the cost-effectiveness analyses. However, Dmab emerges as a cost-effective alternative in the management of PMOP.

8.2. In cancer

A similar debate has arisen concerning the cost-effectiveness of Dmab relative to zoledronic acid, for which a generic form exists, in relation to protection against SREs in women and men with bone metastases. In the case of PMOP, one determining effect of Dmab derives from its efficacy in preventing or delaying SREs. The higher cost-effectiveness of Dmab against zoledronate has been supported [41] and opposed [42] for men with prostate cancer in the US. The same debate by the same investigators has been reproduced for breast cancer [43–44]. The discussion has been replicated for concerns about bone metastases from solid tumours. Two systematic reviews conclude that there are disagreements that are influenced by the differences in the methods or by the parameters considered for evaluation [45–46].

9. Summary of recommendations

– As stated in our previous consensus about PMOP [1], diet and healthy lifestyle are essential measures in prevention or as adjuvants of treatment. Adequate amount of calcium and vitamin D intake (1200 mg of calcium and 800 units of vitamin D daily from diet and supplements, Grade 2B) should be accompanied

by lifestyle measures (physical activity, smoking cessation, prevention of falls, and avoidance of excessive alcohol consumption, Grade 1A).
- Dmab is a highly effective and safe treatment for patients with PMOP and a high fracture risk. It significantly reduces the risk of vertebral, non-vertebral, and hip fractures (Grade 2A).
- Dmab can be used as a first-line therapy in older women or women at risk of hip fractures. Specifically, we suggest the use of Dmab to improve compliance in women with PMOP and multiple risk factors, those with a history of fractures or renal failure, and those who cannot tolerate other treatments or for whom other treatments have failed. Different studies have concluded that Dmab may be a cost-effective alternative.
- The optimal duration of treatment with Dmab remains undefined. Accordingly, we recommend periodic reassessment on an individual basis. Changing to alternatives may be influenced by variables like the duration of treatment, age and characteristics of the patient.
- Dmab may offer advantages in patients with breast cancer with osteopaenia due to treatment with aromatase inhibitors.
- Dmab can be considered as an alternative to zoledronic acid in women with bone metastases from breast cancer in which treatment with an osteoclast inhibitor is indicated.

Contributors

Dr. José Manuel Silván, Dr. Antonio Estévez, Dr. Francesc Baró, Dr. José Villero, Prof. Francisco Quereda, Prof Javier Ferrer, Prof. Nicolás Mendoza, Dr. Rafael Sánchez-Borrego and Prof. Antonio Cano declare that they have participated in the literature search and that they selected a list of articles. They were also involved in analysis and interpretation of data and revised the article critically. They have approved the version to be published. Prof. Antonio Cano declares that he was involved in analysis and interpretation of data, revising the article critically for important intellectual content and final approval of the version to be published.

Competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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