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Original article

Efficacy and safety of denosumab for the treatment of osteoporosis: A systematic review

Efficacité et sécurité du denosumab pour le traitement de l'ostéoporose : revue systématique

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Abstract

Denosumab is an anti-RANK ligand (RANKL) monoclonal antibody approved for the treatment of postmenopausal osteoporosis and prevention of skeletal metastasis complications. Administered subcutaneously every 6 months, it reduces the risk of vertebral fracture by 70% and of hip fracture by 40%. Its safety profile is acceptable. Denosumab may be used to treat patients with moderate to severe renal insufficiency. It has anti-fracture activity equivalent to that of zoledronic acid, but no residual effect, and no action at all beyond 6 months. In France, denosumab is reimbursed as a second-line treatment after a first attempt with bisphosphonate.

Keywords: Osteoporosis; Denosumab; Fracture risk; Renal insufficiency; Safety

Résumé

Le denosumab est une biothérapie approuvée pour le traitement de l'ostéoporose ménopausique et pour la prévention des complications des métastases osseuses. C'est un anticorps monoclonal dirigé contre le Rank ligand. Il agit pendant 6 mois après une injection sous-cutanée. Chez la femme ostéoporotique ménopausée, il réduit le risque de fracture vertébrale de 70 % et celui du col du fémur de 40 %. Sa sécurité d'emploi est satisfaisante. Il peut être utilisé chez les sujets porteurs d'une insuffisance rénale modérée à sévère. Le denosumab a des actions anti-fracturaires équivalentes à l'acide zolédronique. Il n'a pas d'action rémanente et son effet disparaît au-delà de 6 mois d'action. Le denosumab est un traitement de deuxième ligne de l'ostéoporose ménopausique sévère. Il est remboursé après une première tentative de traitement par les bisphosphonates.

Mots clés : Ostéoporose ; Denosumab ; Risque fracturaire ; Insuffisance rénale ; Tolérance

1. Introduction

The ongoing development of treatments for postmenopausal osteoporosis has recently resulted in the introduction of several new pharmacological classes: SERMs, bisphosphonates, parathyroid hormone analogs and strontium ranelate. Agents that have disappeared from the pharmacopoeia include fluoride salts and anabolic steroids.

Denosumab has a powerful and prolonged inhibitory effect on bone remodeling [1]. It is approved for treatment of postmenopausal osteoporosis, of androgen deprivation in prostate cancer therapy and prevention of skeletal metastasis complications.

In its anti-osteoporotic indication, it is administered subcutaneously at a dose of 60 mg every 6 months [2]. It acts in a similar manner to osteoprotegerin, by inhibiting RANKL (Fig. 1). Denosumab, a fully humanized monoclonal antibody, has a specific affinity for RANKL, but no activity

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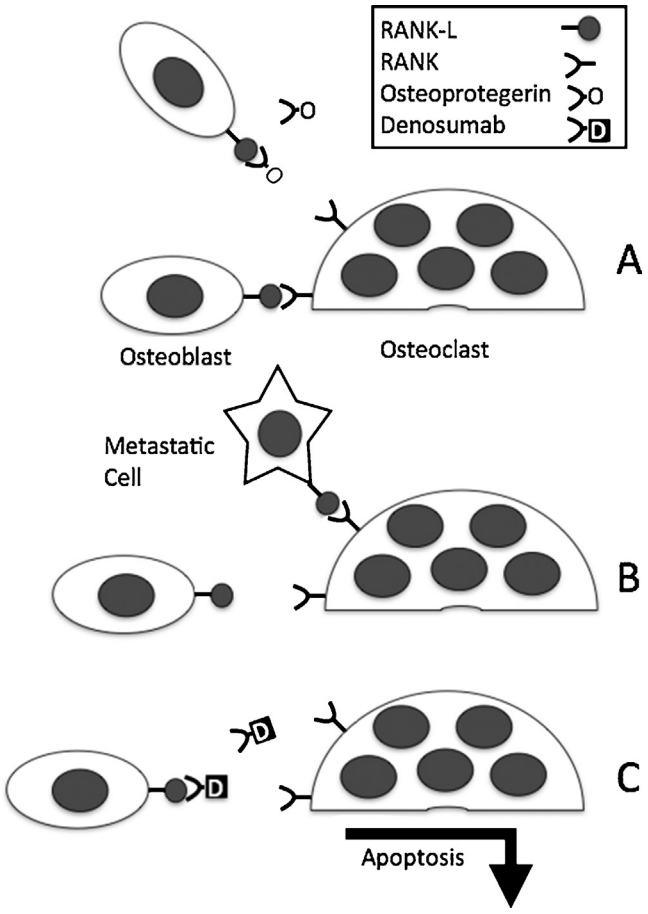

Fig. 1. Regulation of osteoclasts by RANK-RANK ligand pathway. A. Modulation by osteoprotegerin in physiology. B. By metastatic cells. C. Denosumab-induced apoptosis.

against tumor-necrosis-factor related apoptosis inducing ligand (TRAIL) [3].

The key investigation in the development of denosumab was the pivotal study versus placebo, fracture reduction evaluation of denosumab in osteoporosis every 6 months (FREEDOM) [4]. Several less ambitious studies have focused on the control of osteoporotic risk after breast cancer or prostate cancer, and comparisons with various bisphosphonates [5–17]. Our work provides a summary of the results of published clinical trials to date.

2. Methodology

2.1. Data sources and search strategies

We conducted a review of the medical literature to identify all studies that evaluated the effect on bone of denosumab administered every 6 months. The studies focus on the evolution of fracture risk, bone mineral density, biochemical markers of bone remodeling, and side effects of the molecule. The search was conducted in the Medline and Cochrane databases with no date limitation and using the following keywords: denosumab and (bone or bone mineral density and bone microarchitecture or osteoporosis or fracture or fracture risk or bone metabolism or biochemical markers of bone metabolism or side effects or adverse reactions) in women or in men. Reference lists of retrieved studies were also analyzed. The search was limited to publications in English and French. Articles identified from titles and abstracts as being of interest were analyzed using the full manuscripts.

2.2. Study selection

In order to be included in our literature review, studies were required to meet the following criteria: cohort study, prospective, randomized phase II and III trials evaluating the effects of denosumab on fracture risk, bone mass, biochemical markers of bone remodeling and side effects in women and men. We excluded clinical cases, literature reviews, commentaries, letters to the editor, experimental studies, phase I studies, and retrospective and observational studies.

2.3. Data extraction and quality evaluation

An independent investigator reviewed each item included and extracted its general characteristics, such as the names of the authors, year of publication, type, method and duration of follow-up, characteristics of the population studied, parameters of interest, sample size, comparison groups, the evolution of the parameters studied and the type of statistical analysis.

3. Results

In total, 20 trials were identified: five phase II [2,8,18–20], ten phase III [1,4–7,9–11,21,22] and five phase III open label studies [12–15,17]. They involved 14,248 women with postmenopausal osteoporosis, 252 women receiving adjuvant aromatase inhibitor therapy for non-metastatic breast cancer, 301 men with osteoporosis and, finally, 1468 men receiving adjuvant treatment with anti-androgen for non-metastatic prostate cancer. Denosumab was evaluated in comparison to placebo in 13 studies [1,2,4–9,18–22], alendronate in seven [5,8–11,17,22] and in one study each against zoledronic acid [12], ibandronate [13], risedronate [14] and teriparatide [15,16]. Table 1 describes the characteristics of the eligible studies.

3.1. Denosumab and fracture risk

In the FREEDOM study, the risks of vertebral and non-vertebral fracture were significantly reduced in the denosumab group. Risk reductions at 12, 24 and 36 months were 61%, 71% and 68% for vertebral fractures and 16%, 21% and 20% for non-vertebral fractures, respectively. At 3 years, the reduction in the risk of hip fracture was 40% (RR = 0.6, 95% CI = [0.37–0.97]) [4,23]. Wrist fracture risk decreased with the severity of osteoporosis [24]. This trend continued during the extension phases of FREEDOM to 5 years [25] and 6 years [26], with reductions of 37% and 45% in vertebral fractures and 58% and 50% in non-vertebral fractures, respectively.

The reduction in the risk of vertebral fracture at 36 months was seen in all patient groups regardless of age, bone mineral