

Review article

Review on the comparison of effectiveness between denosumab and bisphosphonates in post-menopausal osteoporosis

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Abstract

Objectives: Osteoporosis is a rapidly rising cause of concern for elderly patients. Various classes of drugs are available in the market. Bisphosphonates are considered as a first-line therapy for the prevention and treatment. Denosumab is an antiresorptive agent which is a RANK ligand inhibitor. There is a scarcity of comparison between these two classes of drugs. The aim of this study is to compare efficacy of Bisphosphonates and Denosumab in various parameters.

Methods: Literature search was done for randomized controlled trials (RCTs) comparing bisphosphonates with denosumab. RCTs with a treatment period of at least one year with a baseline bone mineral density (BMD) and bone turnover markers (BTM) and follow up values at one year were included in the study. All included studies were also analysed for complications. The study has also been registered in PROSPERO International prospective register of systematic reviews.

Results: A total of five RCTs were identified providing data on 3751 participants. In all five studies, the BMD changes at both hip and spine were statistically significant in favour of denosumab. Result was similar in three studies that studied BMD changes at the wrist. Denosumab also produced significant reduction in BTM as early as one month, but at one year there was no difference compared to the bisphosphonates. There was no statistically significant differences in the complication rates.

Conclusions: Though both bisphosphonates and denosumab were effective with similar side effects, the latter was statistically superior in increasing the BMD and reducing the BTM.

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Keywords: Denosumab; Bisphosphonates; Post-menopausal osteoporosis; Bone mineral density; C-telopeptide

1. Introduction

Postmenopausal osteoporosis is a disease with features of reduction in the mass of bone, and microscopic changes in the architecture that results in impaired strength of the bone [1]. After menopause, osteoclastic activity exceeds osteoblastic

activity. This results in increased bone resorption which leads to an overall reduction of bone mass. This in turn increases skeletal fragility and risk of developing fractures [2]. Therefore the objective of treatment is to increase bone mass by altering the balance of bone remodelling. Most currently available drugs used to treat osteoporosis such as calcitonin, raloxifene and bisphosphonates, acts as inhibitors to bone resorption.

The two main properties of bisphosphonates resulting in their efficacy are the ability to strongly bind to bone mineral and the inhibition of mature osteoclasts [3]. Once the bisphosphonate is strongly attached to bone, this results in

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selective uptake by the bone mineral. After this, the bisphosphonates act at the sites of bone resorption by entering and inhibiting the mature osteoclastic cells.

Receptor activator of nuclear factor kappa-B ligand (RANKL), a cytokine secreted by bone marrow stromal cells, osteoblasts and T cells, is essential to induce osteoclast differentiation [4]. In post-menopausal osteoporosis with estrogen deprivation there is raised expression and production of RANKL, resulting in increased osteoclast activation and increased bone resorption. Reducing the number of osteoclasts by decreasing differentiation of precursor cells is one of the treatment modalities of hyper-resorptive bone diseases. Denosumab is one such fully human monoclonal antibody that can bind and inhibit RANKL.

There are numerous studies on the efficacy of bisphosphonates and other medications available for osteoporosis including denosumab. But there are very few randomised controlled trials (RCT) directly comparing bisphosphonates and denosumab. The aim of this systematic review was to identify studies that simultaneously compared bisphosphonates and denosumab and to analyse the efficacy in various parameters.

2. Materials and methods

Search Strategy: A search was done in several databases such as Pubmed Central, Cochrane CENTRAL and MEDLINE. The search was restricted to articles in English language. The search terms used were osteoporosis, post-menopausal, denosumab, bisphosphonates, bone mineral density and C-telopeptide. A filter for RCTs was also used. The Cochrane handbook of systematic reviews of interventions was referred to identify any discrepancies and biases in randomization, allocation concealment, blinding and missing data in the included RCTs [5].

Inclusion criteria: All RCTs directly comparing bisphosphonates with denosumab in post-menopausal osteoporosis were included. Only fully published reports with initial and final bone mineral density (BMD) and bone turnover markers (BTM) were included. CONSORT check list was used to critically appraise the included studies and all the studies fulfilled the criteria.

Statistical analysis: Data extracted included study design, selection criteria, population demographics, type of intervention, initial and final BMD, initial and final BTM as well as complications if any. Results of all the included studies were described in a table format. Key outcomes were percentage changes in BMD, BTM and complications.

3. Results

A total of six RCTs were identified. In one study, the participants had used denosumab for a long period and then stopped before restarting the therapy [6]. This RCT was excluded from the current study. A total of five RCTs were identified with a total of 3751 participants. The characteristics of the included studies are summarized in Table 1. Three studies compared denosumab with alendronate [7–9] and one study each for denosumab vs. risedronate [10] and denosumab vs. ibandronate [11]. All studies were checked to identify any discrepancies and biases in randomization, allocation concealment and blinding based on CONSORT checklist. No possible bias was found.

In one included RCT, subjects received variable doses of denosumab, viz. 6, 14 or 30 mgs subcutaneously (s/c) every three months or 14, 60, 100 or 210 mgs s/c every six months [7]. In all the other studies, subjects received denosumab in a dose of 60 mg s/c every six months.

3.1. Bone mineral density

Baseline BMD in each of the study was noted for both the groups of subjects. All the five included studies recorded BMD changes at the lumbar spine and hip. In addition to this, four of the studies recorded BMD changes at the femoral neck and three studies at the distal radius. All the five studies reported improvement in BMD at the lumbar spine and hip after treatment in both groups but the improvement was statistically significant in favour of denosumab. Four studies reported statistically significant improvement in BMD at the femoral neck in favour of denosumab. Three studies also reported statistically significant improvement in BMD at the distal radius, again in favour of denosumab. The results are shown in Table 2.

Table 1
Characteristics of included studies.

Study	Study design	Drugs	Dosing	Number of patients	Age of patients in years (SD)	Treatment duration (Mo)
Lewiecki EM et al. J Bone Miner Res. 2007 [7]	Randomized	Denosumab	Varying doses s/c every 3 or 6 months	319	62.3 (8.0)	24
Brown JP et al. J Bone Miner Res. 2009 [8]	Double blind	Alendronate	70 mgs orally per week	47	62.8 (8.2)	12
	Randomized	Denosumab	60 mgs s/c every 6 months	594	64.1 (8.6)	
Nakamura T et al. J Clin Endocrinol Metab. 2014 [9]	Double blind	Alendronate	70 mgs orally per week	595	64.6 (8.3)	24
	Randomized	Denosumab	60 mgs s/c every 6 months	414	69.9 (7.4)	
Roux C et al. Bone. 2014 [10]	Double blind	Alendronate	35 mgs orally per week	204	70.2 (7.3)	12
	Randomized	Denosumab	60 mgs s/c every 6 months	422	67.8 (7.0)	
Recknor C et al. Obstet Gynecol. 2013 [11]	Open label	Risedronate	150 mgs orally per month	402	67.7 (6.8)	12
	Randomized	Denosumab	60 mgs s/c every 6 months	398	67.2 (8.1)	
	Open label	Ibandronate	150 mgs orally per month	356	66.2 (7.8)	

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