The Bisphosphonates versus Denosumab Efficiency in Postmenopausal Osteoporosis Treatment

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ABSTRACT ***Introduction.*** Osteoporosis is a frequently ignored disease, that has the potential to develop an adverse outcome, leading to complications that lower patients' quality of life. Postmenopausal osteoporosis is a well-studied subject, being a disease with an increasing prevalence. However, there is a large number of drugs to choose from for the treatment of postmenopausal osteoporosis. Bisphosphonates are the most used therapeutic choice but, with an almost 10-year clinical experience, RANKL inhibitor Denosumab is becoming more frequently used in practice, with great results. The main purpose of this review is to evaluate the efficacy of bisphosphonates compared with that of Denosumab by analyzing different parameters.

Matherials and methods. We included randomized studies that directly compared bisphosphonates to Denosumab after 1 year of treatment, which included data regarding the bone mineral density (BMD) and bone turnover markers (BTM) measured at baseline and after 12 months.

Results. Seven randomized studies were included in this review, combining a total of 4535 patients. In all 7 studies the changes in lumbar spine bone mineral density were statistically significant in favor of Denosumab. Denosumab also produced a decrease in bone turnover markers as early as 1 month from the beginning of the treatment. After 12 months of treatment the reduction percentage of BTM were similar between the two groups. The rate of adverse effects' occurrence is similar between the two groups.

Conclusion. Denosumab treated patients present an increase in bone mineral density after 12 months of treatment when compared to bisphosphonates. Both therapies have a similar reduction of bone turnover markers. The rate of adverse effects' occurrence during the 12 months of monitoring were also similar between the two drugs.

Keywords: ***postmenopausal osteoporosis, bisphosphonates, Denosumab, bone mineral density, bone turnover markers.***

Introduction

Osteoporosis is a systemic skeletal disease characterized by reduced bone mass and bone tissue microarchitecture deterioration, which leads to a consecutive increase in bone fragility. Frequently it is an asymptomatic disease until a fracture occurs [1]. Osteoporosis has a higher prevalence among white women [1,2], being a preventable postmenopausal disease [3].

After menopause, the osteoclastic activity overcomes the osteoblastic activity. This leads to the increase of bone resorption, followed by a global reduction in bone mass. This reduction of bone mass is subsequently followed by an increase in skeletal fragility and fracture risk [4].

The objective of the pharmacological treatment is to increase bone mass through modification of bone remodeling equilibrium. Until present day, none of the drugs used in the treatment of postmenopausal osteoporosis can fully restore skeletal density.

The disease progression can be slowed by an early pharmacological treatment [5].
Bisphosphonates are the most frequently used drugs in osteoporosis treatment. They are used both for the prevention and for the pharmacological treatment of this disease, orally or intravenous[5]

Table I. Major recommandations for clinician, adapted after the AACE/ACE Guidelines [6]

General recommandations	
Counseling regarding the risk of osteoporosis and fractures	Adequate intake of vitamin D and calcium
Physical exercise	Risk factors evaluation
Testing for bone mineral density (BMD) evaluation	
Women aged 70 and above and men aged 80 and above with a T score ≤ -1	Women between 65 and 69 years and men between 70 and 79 years with a T score ≤-1.5
Postmenopausal women and men aged 50 and above with selected risk factors	
Monitoring	
Bone mineral density evaluation every 1-2 years after treatment initiation and every 2 years after	Biochemical markers evaluation for assessing therapeutic efficiency
Pharmacologic treatment initiation	
Patients with clinical or asymptomatic fractures	Patients with a T score ≤-2.5
Postmenopausal women or men aged 50 and above with osteopenia (T score between -1 and -2.5) and a 10 years hip fracture probability ≥3% or a 10 year osteoporosis related fracture ≥20% based on the absolute risk model of fracture approved by WHO (www.NOF.org; www.shef.ac.uk/FRAX)	

Bisphosphonates have a pirophosphate-like structure, which are compounds incorporated in the bone matrix. Bisphosphonates suppress the osteoclastic Denosumab is a fully human monoclonal antibody for the receptor activator of nuclear factor kappa-B ligand (RANKL). Denosumab adheres to RANKL, leading to the inhibition of kappa-B nuclear factor's ability to initiate the growth of osteoclastic precursors and bone resorption realized by mature osteoclasts. RANKL holds an important role in the final process of osteoclastic formation, activity and survival [7,10,11].
Bone metabolism is a continual cycle of bone formation and resorption. These two processes are regulated by the equilibrium between endogenous (cytokines, hormones, growth factors) and exogenous (the mechanical loading process) factors [12]. There are well known blood and urinary molecules that can measure bone metabolic activity. These markers are usually divided into two categories: bone formation biomarkers derived from osteoblastic activity (bone specific alkaline activity and number by inducing apoptosis. Through this effect, bisphosphonates reduce bone absorption, thus increasing bone mineral density [7,8,9].
phosphatase, osteocalcin, N-terminal propeptide and C-terminal propeptide type I procollagen) and bone resorption biomarkers derived from type I collagen degradation (N-terminal telopeptide, C-terminal telopeptide etc.) [13].
Although there are many studies in the literature which assess bisphosphonates efficacy, as well as different other drugs used in the treatment of postmenopausal osteoporosis, including Denosumab [14,15,16], the number of randomized controlled studies (RCT) is low [18-24].
The main purpose of this systematic analysis is to identify the studies that have compared the bisphosphonate and Denosumab efficacy and to establish which of these two treatments is better at increasing the bone mineral density of postmenopausal osteoporosis after 12 months.

Materials and methods

The present analysis was conducted according to the PRISMA Statement [17]. The studies included in the analysis were searched in several databases (PubMed Central, Medline, Embase and Scopus) since their founding until february 2017. The search was limited to articles written in English. The search terms used were postmenopausal osteoporosis, Denosumab, bisphosphonates, bone mineral density and bone turnover markers. A filter for randomized controlled studies (RCT) and human studies was also used.

Inclusion criteria

All RCTs that directly compared bisphosphonates to Denosumab, used for at least 1 year in the treatment of postmenopausal osteoporosis were screened. Only fully published reports were included in the analysis, which contained data about the baseline and 12 months values of bone mineral density (BMD) and bone turnover markers (BTM). The Consort checklist was used to critically evaluate the RCTs included in the present study.

Exclusion criteria:

Analyses or meta-analyses, conference papers and inconsistent data articles or with fewer than 12 months follow-up on the patients.

Statistical analysis:

The extracted data included study design, selection criteria, population demographics, type of intervention, baseline and 12 months BMD values, baseline and 12 months BTM values and the adverse effects that occurred due to the treatment. The results were processed in Review Manager 5.3.

Results

Seven RCTs [18-24] were included in the present analysis that presented the necessary inclusion criteria. A total of 4535 participants were included in these 7 RCTs. Five studies compared the efficacy of Denosumab vs Alendronate treatment [18,19,21,22,23], one study compared Denosumab with Risedronate [20] and one study compared Denosumab with Ibandronate [24]. All studies were verified to identify the eventual discrepancies and prejudices in randomization using the Consort checklist. No such discrepancies or prejudices were identified.

We build a Flow diagram to present the aforementioned studies selection process (Fig. 1).

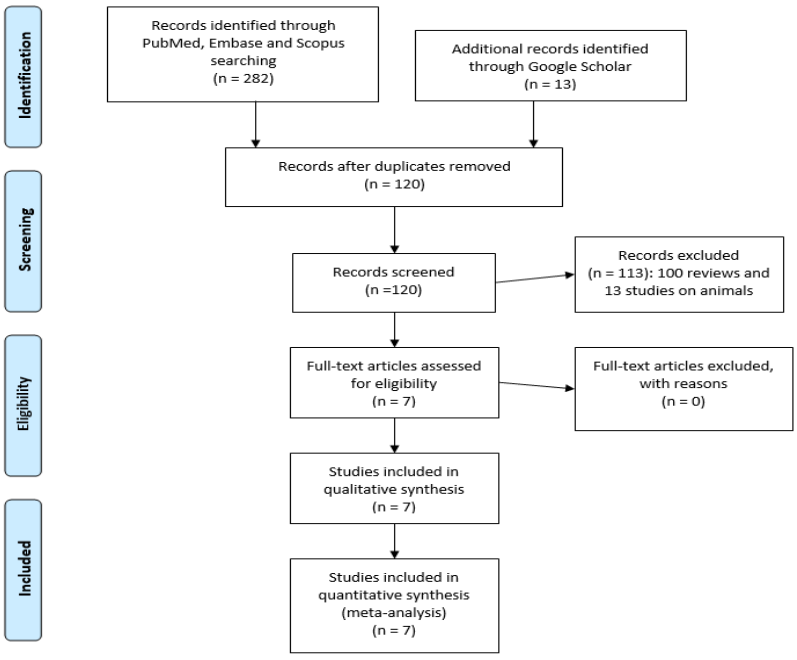

Figure 1. Flow diagram of the selected studies, after the PRISMA Statement [17]

The demographic characteristic and the DXA test results at baseline as well as after 12 months of treatment are synthesized in Table II.

Table II. Patient characteristics of the included studies and BMD values measured on lumbar spine before and after 12 months treatment

First author (year)	Number of patients - Denosumab	Number of patients - bisphosphonates	Mean age denosumab/ bisphosphonate	Baseline BMD values measured at lumbar spine Denosumab	Mean percentage changes of BMD values measured at lumbar spine at 12 months Denosumab	Baseline BMD values measured at lumbar spine bisphosphonates	Mean percentage changes of BMD values measured at lumbar spine at 12 months bisphosphonates
Lewiecki M (2007)	319	47	62.3±8/62.8±8.2	-2.1±0.1	6.51	-2.15±0.15	5.5
Nakamura T (2014)	449	230	69.9±7.36/70.2±7.31	-2.78±0.89	9.1	-2.69±0.94	7.5
Roux C (2013)	435	435	67.8±7/67.7±6.8	-2.2±1.2	3.4	-2.3±1.1	2.3
McClung M (2006)	47	47	63.1±8.1/62.8±8.2	-2.2±0.7	4.85	-2.0±0.9	3.6
Kendler D (2009)	253	251	66.9±7.8/68.2±7.7	-2.64±0.75	3.03	-2.62±0.79	1.85
Brown JP (2008)	594	595	64.1±8.6/64.6±8.3	-2.57±0.75	5.3	-2.57±0.75	4.2
Recknor C (2013)	417	416	67.2±8.1/66.2±7.8	-2.5±0.9	4.1	-2.5±0.8	2

Bone Mineral Density (BMD)

All studies measured baseline lumbar spine BMD for both groups of patients (Denosumab and bisphosphonate treated). The 7 RCTs [18-24] registered changes in lumbar spine BMD values. Five studies [19,20,22,23,24] also recorded changes in femoral neck BMD values and five studies [18,19,21,22,23] in distal radius BMD values. Both groups obtained an improvement in lumbar spine BMD values after 12 months of treatment in every study, but the improvement was statistically significant in favor of Denosumab. Five studies [19,20,22,23,24] recorded a statistically significant improvement in favor of Denosumab in femoral neck BMD values and five studies recorded a significant improvement, again in favor of Denosumab, in distal radius BMD values [18,19,21,22,23]. Using Review Manager 5.3, we conducted an analysis that shows that in all 7 studies Denosumab was statistically superior to bisphosphonates after 12 months of treatment. In this analysis we took into account only lumbar spine BMD values and for the purpose of consistency and lowering the bias risk, we used an unitary standard deviation (DS) due to the fact that not all study reported this value. The Forrest Plot graphic is presented in Figure 2.

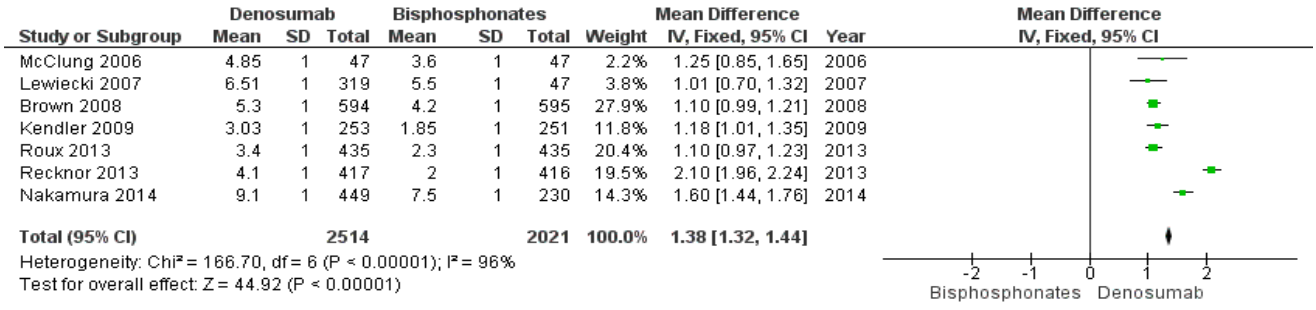

Figure 2. 12 months efficacy comparions between bisphosphonates and Denosumab therapy

Bone Turnover Markers

All seven included studies [18-24] measured the baseline values of bone turnover marker C-telopeptide, as well as the procentual change of this marker after 12 months of treatment. Four studies found a statistically significant reduction of C-telopeptide in favor of Denosumab

[18,20,22,24]. Two studies didn't find any significant difference after 12 months of treatment between the two drug classes [21,23], and a single study reported superior results in favor of bisphosphonates [19]. These results are presented in Table III.

Five of the included studies [18,19,21,22,23] reported the 12 month reduction in bone specific alkaline phosphatase. Of these five studies, three [21,22,23] found Denosumab statistically superior to bisphosphonates, while two [18,19] didn't find any significant difference between the two classes after 12 months of treatment.

Table III. Baseline bone turnover markers and their procentual change at 12 months of treatment

Study	Treatment	Baseline value of C -telopeptide (ng/ml)	Changes in C-telopeptide after treatment	Baseline value of NTx-telopeptide	Changes in NTx-telopeptide after treatment	Baseline value of bone alkaline phosphatase	Changes in bone alkaline phosphatase after treatment
Lewiecki, 2007	Denosumab	0.649	-70%	63.8	-35%	12.35	-60%
	Alendronat	0.675	-67%	64.92	-45%	12.44	-62%
Brown JP, 2009	Denosumab	0.705	-74%	-	-	54.17	-72%
	Alendronat	0.654	-76%	-	-	50.5	-65%
Nakamura T, 2014	Denosumab	0.64	-64%	-	-	-	-50%
	Alendronat	0.61	-72%	-	-	-	-53%
Roux C, 2014	Denosumab	0.32	-60.60%	-	-	-	-
	Risedronat	0.33	-22.50%	-	-	-	-
Recknor, 2013	Denosumab	0.4	-59.90%	-	-	-	-
	Ibandronat	0.4	-42%	-	-	-	-
McClung, 2006	Denosumab	0.60±0.29	-60%	-	-	11.4±6.2	-66%
	Alendronat	0.68±0.26	-62%	-	-	12.4±6.2	-61%
Kendler, 2009	Denosumab	0.187	-11%	-	-	21.24	-13%
	Alendronat	0.207	10%	-	-	22.52	-0.50%

Complications

Several adverse effects were recorded, including cardiovascular side effects, gastroenterologic side effects, hypocalcemia, osteoarthicular side effects, malign or unspeciffied tumors. The majority of studies didn't find any statistically significant differences between the two treatment groups. One study [18] noted the presence of a major difference of gastroenterologic side effect between the Denosumab and Alendronate treated groups (38,8% and 76% respectively). All studies [18-24] recorded the incidence of osteoarthicular side effects, the procentages between the two groups being similar. The results are presented in Table III.

Table IV. The incidence of adverse effects in Denosumab and bisphosphonate treated groups

Study / Adverse events	Lewiecki, 2007		Brown JP, 2009		Nakamura, 2014		Roux, 2014		Recknor, 2013		McClung, 2006		Kendler, 2009	
	Denosumab	Alendronat	Denosumab	Alendronat	Denosumab	Alendronat	Denosumab	Risedronat	Denosumab	Ibandronat	Denosumab	Alendronat	Denosumab	Alendronat
Total adverse events	92.00%	93.50%	80.90%	82.30%	94.30%	94.60%	62.70%	68.30%	59.60%	56.10%	87.30%	91.30%	77.90%	78.70%
Cardiovascular adverse events	10.50%	10.90%	-	-	14.30%	8.70%	-	-	1.70%	0.70%	0.90%	0%	-	-
Infections	34.70%	30.40%	0%	0.20%	60.20%	54.10%	1.20%	1.20%	1.70%	1.50%	0.60%	0%	43.90%	37.30%
Gastrointestinal adverse events	38.80%	76%	27.70%	28.70%	-	-	0.20%	0.20%	1.70%	0.20%	-	-	22.90%	24.10%
Hypocalcemia	-	-	-	-	0.40%	0.80%	-	-	0.20%	0.20%	-	-	-	-
Osteoarticular disorders	73.50%	74%	19.60%	16%	0%	0%	5.40%	4%	3.60%	3.20%	3.80%	2.20%	3.20%	1.60%
Malignancies or unspecified	-	-	3.50%	2.60%	1.90%	0.80%	1.40%	1.90%	1.20%	1.50%	1.90%	0%	3.60%	3.60%

Discussion

From our knowledge the current analysis is the first to compare directly the 12 month efficacy of Denosumab versus bisphosphonates using such a large number of participants.

Denosumab prevents the RANKL interaction with its receptors, leading to the obstruction of osteoclastic maturation, function and survivability [7,10,11]. Bisphosphonates adhere to calcium bone hydroxiapatite, thus reducing bone resorption by affecting the osteoclasts' function and survivability.

There isn't any scientific data regarding the interaction between the osteoclastic

maturation and bisphosphonate until present day.

X-ray osteodensitometry (DXA) is the gold standard for the diagnosis of osteoporosis by analysing the bone mineral density [1].

All analyzed studies [18-24] observed a superior increase of lumbar spine, total hip, femoral neck and distal radius BMD values in the Denosumab treated group (as shown in Table II).

BMD is a frequently used marker to evaluate the efficacy of osteoporosis treatment. Reevaluation using DXA more often than once every 2 years isn't indicated, as the treatment effect is relatively small compared to the test's precision [6]. There hasn't been established any precise and consistent relation between the increase of BMD values and the decrease of specific fractures risk [5].

BTM evaluation is a non-invasive method for the monitoring of treatment efficacy [1]. The biochemical analyses can be used to monitor bone metabolism, the proteins and enzymes being released during the bone formation and resorbtion phases. The analysis of these markers could lead to a very specific and sensitive evaluation of bone formation and resorption rate [25,26]. The used markers are C-terminal telopeptid type I collagen (CTX) for the bone resorption and bone specific alkaline phosphatase (BSAP) for the bone formation [12,13].

BTM reflect the metabolic effect of the used drugs on bone turnover. Bone resorption inhibition leads to a decrease of bone resorption markers followed by a plateau. By contrast, bone formation continues at the same rate. BTM changes depend on the drug administered. Denosumab administered subcutaneously inhibits the bone resorption as early as 12 hours after administration. Bisphosphonates administered intravenously inhibit bone resorption and lower resorption markers more rapidly than oral administration [25,26,27].

The data we obtained are consistent with the data obtained by other meta-analyses [28,29]. We can therefore affirm that Denosumab is more efficient than bisphosphonates in increasing the bone mineral density values after 12 months of treatment. Neither of the drug classes had a decreased rate of fracture incidence. Future inquiries will need to include a longer patient monitorization to provide a higher accuracy of results.

Conclusion

The administration of Denosumab in the treatment of postmenopausal osteoporosis leads to a superior increase of bone mineral density and decrease of bone turnover markers compared to bisphosphonates. The rate of adverse effects' occurrence is similar between the two therapies. In order to establish a clear difference future studies will need to monitor patients for more than 24 months.

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