Ranking antireabsorptive agents to prevent vertebral fractures in postmenopausal osteoporosis by mixed treatment comparison meta-analysis

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Abstract. – **INTRODUCTION:** Bisphosphonates are considered as a first-line therapy for the prevention and treatment of osteoporosis, showing in double-blind, randomized, controlled trials a significant reduction of incidence of new vertebral fractures compared to placebo. Recently also, Denosumab has been shown to reduce the appearance of new vertebral fractures by blocking RANK. There are not head to head comparative studies between the above mentioned drugs. Mixed treatment comparison, an extension of traditional meta-analysis, is able to compare simultaneously several drugs across a range producing a synthetic evidence of efficacy and a range of probability as to the best treatment.
OBJECTIVES: The aim of this study is to simultaneously compare alendronate, risedronate, ibandronate, zolendronate and denosumab in the prevention of OP vertebral fractures in a Bayesian meta-analysis for assessing indirect comparisons.
MATERIALS AND METHODS: A search for randomized controlled trials involving alendronate, risedronate, ibandronate, zolendronate and denosumab was conducted using several databases. Randomized controlled trials (RCTs) with a double blind treatment period of at least 3 years were included. Men and Glucorticoid Induced osteoporosis, RCTs having as primary or secondary endpoints continuous values as body mineral density (BMD) and studies comparing different dosing regimens of the same agent, which are not used in clinical practice, were excluded. Only fully published reports were considered.
RESULTS: A total of 9 RCTs were identified providing data on 31,393 participants. Zolendronate had the highest probability (52%) of being the most effective treatment towards placebo, followed by denosumab (46% probability), ibandronate and then alendronate and risedronate against placebo.
CONCLUSIONS: Although the mixed treatment comparisons among alendronate, risedronate, ibandronate, zolendronate and denosumab did not show a statistically significant difference, this analysis suggests that zolendronate, compared to placebo, is expected to provide the highest rate of reduction in vertebral fractures affecting osteoporosis affected patients.

Key Words:
    Bisphosphonates, Vertebral fractures, Postmenopausal osteoporosis, Mixed treatment comparison.

Introduction

Osteoporosis is an increasing concern for older adults as fragility fractures can significantly affect overall health and quality of life representing a public health challenge. Epidemiological data worldwide have consistently demonstrated that the annual incidence of fragility fracture increases with age[1-2]. The burden of fracture is expected to increase with an aging population. Hence, in an aging, osteoporotic population, fracture prevention through the optimisation of drug administration should be an important goal.

Vertebral fractures (VE) are the more frequent kind of fracture in postmenopausal women, with an annual risk of 0.24% for a 50 year old woman increasing to 0.89% for an 85 year-old woman[3,4].

About 25% of patients with one vertebral fracture undergo a second vertebral fracture during the following year[5]. Patients with a previous vertebral fracture have an increasing risk (about 50%) of development of a femoral fracture[6]. Vertebral fractures increase the relative risk of developing any non vertebral fracture, just as any non vertebral fracture increases the relative risk of developing any VE[7-8].

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Previous fractures are the most important risk factor in the development of new fractures; this risk factor is not related to bone mineral density (BMD) and is strongly considered in the count of absolute relative risk of fracture by the recent algorithm proposed by WHO[9]. Also parental history for vertebral or non vertebral fracture is not related to BMD risk factor in the development of new fractures[9].

Reduction in the incidence of new VE is the necessary goal to obtained for the registration of any new drug in the primary or secondary prevention of osteoporosis. Bisphosphonates are considered as a first-line therapy for the prevention and treatment of osteoporosis; in fact alendronate, risedronate, ibandronate and zolendronate evidenced in double-blind, randomized, controlled trials (RCT) a significant reduction of the incidence of new VE compared to placebo[10-17].

Reductions in relative risk (RR) of morphometric vertebral fracture ranged from 41% to 70% over 3 years in the RCT conducted on bisphosphonates. These data concern only the effect of any single bisphosphonate compared to placebo, but there are no data from head to head RCT focused on reduction of incidence of new vertebral fracture.

Recently denosumab was launched in the UK and in the USA for the treatment of osteoporosis in post-menopausal women. Denosumab is a new antiresorptive agent with a novel mechanism of action. Indeed, denosumab is a human monoclonal antibody that targets and binds with high affinity and specificity to Receptor Activator of Nuclear Factor KB (RANK) ligand, preventing activation of the RANK receptor, which is found on osteoclast precursors and osteoclasts[18,19]. By blocking RANK, Denosumab reduces incidence of new vertebral and non-vertebral fractures. In the Freedom study[20] denosumab, compared to placebo, decreased the RR of new morphometric VE of 68% after 3 years of treatment.

In literature we can find several attempts to compare efficacy of different bisphosphonates. A kind of comparison is based on different increases in BMD due to different molecules[21]. Bone mineral density is a surrogate value that is correlated to reduction in fracture risk, but, as clearly demonstrated in literature, is only one of the determinants of the antifracture activity of bisphosphonates[22,23].

Another kind of comparison is based on post-marketing data, concerning a large population of osteoporotic patients (OP) treated with bisphosphonates, evaluated in retrospective cohort studies[24-26]. Observational retrospective studies show several limits and can be useful only to support data from RCT.

Meta-analysis seems to be the more useful way to compare data from different RCT about efficacy of bisphosphonates; several examples of such meta-analysis are present in literature[27,28]. Despite the number of trials and meta-analyses available it is often quite difficult to compare the efficacy of bisphosphonates. Due to the limitations of standard pairwise meta-analysis, it is very difficult to synthesize these studies and to perform a valid comparison. Conclusions from these meta-analyses are necessarily weak, inducing doubt about therapeutic choice in the clinical practice, which requires a concise synthesis of the data as an important component in facilitating evidence based decision making. The complexity of the evidence on bisphosphonates, the absence of head to head RCT and the limitations of standard pair wise meta-analysis drive the need for a more flexible approach to evidence synthesis that is better able to take into account the data of all available treatments.

Mixed treatment comparison (MTC) is an extension of traditional meta-analysis which includes multiple different pair-wise comparisons across a range of interventions. MTC is a valuable alternative to synthesize evidence when the interest is to compare multiple interventions[29]. A Bayesian approach to a MTC can be considered as the method of choice because it allows for a probabilistic interpretation and, therefore, leads naturally into the decision making context[30,31]. An additional benefit of mixed treatment comparison analyses is that it is possible to rank treatments in terms of their likelihood of being the most effective treatment.

The mixed treatment comparison approach has been used recently in the analysis of stroke prevention[32], antidepressants[33], psychological interventions in heart disease[34] and biological agents in rheumatoid arthritis[35,36].

This MTC seeks to simultaneously compare alendronate, risedronate, ibandronate, zolendronate and denosumab in the prevention of OP VE by only one Bayesian meta-analysis assessing indirect comparisons.

Materials and Methods

Interventions

Search strategy and selection criteria: a search for randomised controlled trials involving alen-

dronate, risedronate, ibandronate, zolendronate and denosumab was conducted using several databases (CENTRAL, CINAHL, Embase, HMIC, MEDLINE and PsycINFO).

Each database was searched from inception to May 2010 and restricted to English language papers. The search was kept particularly broad with search terms on osteoporosis, VE, prevention, and a filter for randomised controlled trials was used in order to increase sensitivity. Additional papers were found by searching the references of retrieved articles, tables of contents of relevant journals, previous systematic reviews and meta-analyses about bisphosphonate in OP.

In order to evaluate quality of studies and eventually identify discrepancies and biases for performing a MTC, randomization, allocation concealment, blinding, missing data and selective reporting of results were analyzed by mean of Cochrane Handbook for Systematic Reviews of Interventions[37].

Inclusion Criteria

Randomized double blind controlled trials with a treatment period of at least 3 years were included. Only full-published reports including women affected by postmenopausal osteoporosis were considered; letters and abstracts were excluded. Only RCTs having as primary or secondary endpoints both clinical and morphometric VE were included.

Exclusion Criteria

RCTs studying MenOP and Glucorticoid Induced OP or having as primary or secondary endpoints continuous values as BMD were excluded. Also studies comparing different dosing regimens of the same agent, which are not used in clinical practice, were not included.

Intervention

The intervention of at least one study group included one of the following drugs and dosing regimens in clinical use: alendronate, risedronate, ibandronate, zolendronate and denosumab.

Statistical Aanalysis

All data were extracted regarding study design, selection criteria, study population characteristics, intervention, and vertebral fracture risk from all studies that met the inclusion criteria.

WinBUGS software[38] was used to perform the mixed treatment comparisons based on the Markov Chain Monte Carlo (MCMC) method.

These methods represent a generalization of meta-analysis and they make possible comparisons not addressed within any of the individual primary trials, as they consist of a connected network of RCTs[39]. For example, an indirect comparison of treatments A vs C can be made if these treatments have a common comparator (e.g., A vs B and B vs C). This method preserves within-trial randomization and enables all available direct and indirect comparisons between treatments to be made in one analysis[40].

Results of all trials were analyzed simultaneously by a fixed effect. The primary outcomes were odds ratios (OR) comparing the different treatments, obtained using Gibbs sampling algorithms as implemented in the computer program WinBUGS. The value taken as the MCMC estimate is the mean over iteration sampled starting with the first iteration following burn-in. Convergence was assessed by visual inspection.

In addition, the probability of each treatment to be the most effective treatment is calculated by the proportion of iterations and a particular treatment was found to have the highest relative effect.

Results

A total of 9 RCTs were identified providing data on 31393 participants (for further details of included and excluded studies, see Figure 1). Table I summarizes the study characteristics of these trials. Three trials compared alendronate and placebo, and respectively 2 trials compared risedronate vs placebo, 2 trials zolendronate vs placebo, and only one trial for each one of ibandronate and denosumab vs placebo. All included studies were analyzed for possible differences in randomization, allocation concealing, blinding, missing data, selective reporting of results or other possible bias and no possible bias were identified[37].

All comparisons were judged to have converged after 10,000. These previous iterations were discarded and the analysis was based on a further 90,000 iterations.

Table II summarizes the results of the mixed treatment comparison meta-analysis comparing the various treatments. The odds ratios based on bayesian mixed treatment comparisons are listed together with the probability that each treatment was the most effective.

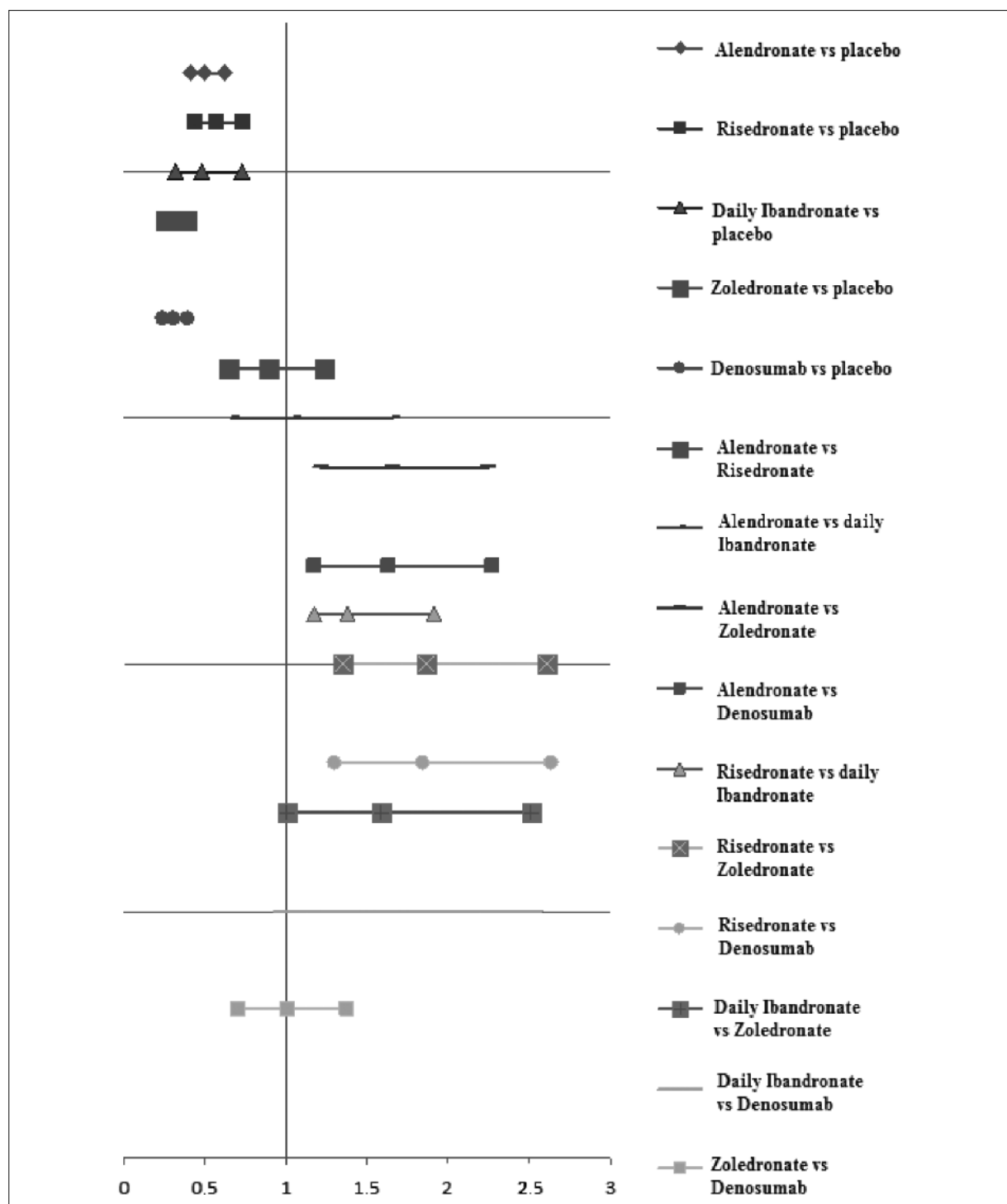Mixed treatment comparisons were largely consistent for most data.

Figure 1. Graphical evaluation of antiresorptive agents' RCTs results obtained by mean of a MTC meta-analysis of included studies.

Zoledronate had the highest probability (52%) of being the most effective treatment towards placebo, followed by denosumab (46% probability), ibandronate (1% probability) and then alendronate and risedronate (0.0% probability). How-

ever, it should be noted that comparisons between any antireabsorptive agent against each other showed that the risk of new VE increased about 1,6 times using alendronate instead of denosumab (OR=1.63 CI95%: 1.17-2.27) or zolendronate

Table I. Included studies' characteristics.

Study	Drugs	Primary end point	Secondary end point	Dosing study	Treatment duration	Number randomized	Treated patients	Patiens' age years	Placebo patients	Placebo age
Dennis M. Black Lancet 1996	Alendronate	Vertebral fractures	Non vertebral fractures	10 mg/daily	36 months	2027	1022	70.7 ± 5-6	1005	71+/-5-6
Liberman N Engl J Med 1995	Alendronate	Vertebral fractures	Non vertebral fractures	5-10-20 mg/daily	36 months	994	909	64	64	
Cummings JAMA 1998	Alendronate	Vertebral fractures	Non vertebral fractures	10 mg/daily	48 months	4432	2214	67.6(6.2)	2218	67.7(6.1)
Harris JAMA 1999	Risedronate	Vertebral fractures	Non vertebral fractures	2.5-5 mg/daily	36 months	2458	1624	69 (7.7)	815	68 (7.2)
Reginster Ost Int 2000	Risedronate	Vertebral fractures	Non vertebral fractures	2.5-5 mg/daily	36 months	1226	815	71 ± 7.0	408	71 ± 7.0
Black. N Engl J Med 2007	Zolendronate	Vertebral fractures	Non vertebral fractures Hip fractures	5 mg annual infusion	36 months	7765	3889	73.1 ± 5.34	3876	73.0 ± 5.40
Lyles. N Engl J Med 2007	Zolendronate	New clinical fractures	Vertebral fractures	5 mg annual Hip fractures Non vertebral fractures	36 months infusion	2127	1065	74.4 ± 9.48	1062	74. ± 9.486
Chesnut, J Bone Min Res 2004	Ibandronate	Vertebral fractures	Non vertebral fractures	2.5 mg/daily	36 months	2496	1964	69 (6)	982	69(6)
Cummings, N Engl J Med 2009	Denosumab	Vertebral fractures	Hip fractures Non vertebral fractures	60 mg s.c every six mounths	36 months	7868	3933		3935	Denosumab

Table II. Main results of Mixed treatment comparison meta-analysis.

Fixed effects mixed treatment comparisons					
Comparisons (outcome new vertebral fractures)	Odds Ratio	95% CrI Low	95% CrI high	Probability best treatment of all treatment compared	Rank
Alendronate vs Placebo	0.501576	0.40657	0.618783	0%	
Risendronate vs Placebo	0.571209	0.440432	0.733447	0%	
Daily Ibandronate vs Placebo	0.481909	0.319819	0.726149	1%	3
Zolendronic Acid vs Placebo	0.304221	0.243655	0.379083	52%	1
Denosumab vs Placebo	0.307586	0.239309	0.394554	46%	2
Alendronate vs Risendronate	0.88692	1.233678	0.637628		
Alendronate vs Daily Ibandronate	1.040811	1.648721	0.657047		
Alendronate vs Zolendronic Acid	1.648721	2.247908	1.20925		
Alendronate vs Denosumab	1.632316	2.2705	1.173511		
Risendronate vs Daily Ibandronate	1.173511	1.915541	1.377128		
Risendronate vs Zolendronic Acid	1.858928	2.611696	1.349859		
Risendronate vs Denosumab	1.840431	2.637944	1.29693		
Daily Ibandronate vs Zolendronic Acid	1.584074	2.50929	1		
Daily Ibandronate vs Denosumab	1.568312	2.534509	0.970446		
Zolendronico Acid vs Denosumab	1.01005	1.377128	0.71177		

(OR=1.65 CI95%: 1.21-2.25). Moreover, risendronate increased significantly the risk of new VE by about 1.8 times in comparison with denosumab (OR=1.84 CI95%: 1.29-2.63) or zolendronate (OR=1.86 CI95%: 1.35-2.61).

Discussion

There are two MTC on bisphosphonates in preventing VF in OP[41,42], but this is the first one including also denosumab in the comparison among available antireabsorptive agents. Denosumab is the first RANK ligand inhibitor to receive approval for human use. In a three-year randomized, double-blind, placebo-controlled trial of 7,808 postmenopausal women ages 60 to 91 years it reduced the incidence of vertebral, nonvertebral, and hip fractures in postmenopausal women with osteoporosis. The aim of this study is to simultaneously compare, by mean of a MTC meta-analysis, alendronate, risedronate, ibandronate, zolendronate and denosumab in preventing OP VE.

The present MTC suggests that Zolendronate and Denosumab appear to be the most effective anti OP treatment, with probabilities respectively of 56% and 42%. However, it should be noted that not all the mixed treatment comparisons between each antireabsorptive agents and other one showed a statistically significant difference. All antireabsorptive agents are more effective than placebo in the prevention of new VE.

The advantage of the present MTC, in comparison with traditional frequentist pair-Wise meta-analysis, is that more of the data is taken into account in one analysis. Moreover, the mixed treatment comparison approach includes the ability to compute the probability that each treatment is the most effective which is a key factor when comparing several interventions.

Previous reviews and frequentist meta-analysis suggested little difference between biphosphonates in preventing new VF; therefore, some Authors[27,28] conclude that all medications were of similar overall effectiveness. In contrast, the present Bayesian meta-analysis identified clear differences between interventions in the probability of being the most effective treatment. Firstly, Zolendronate and then Denosumab were more likely to be the most effective treatments. Our data agree with previous MTC performed by Jansen et al in 2009[41] that demonstrated that zoledronic acid is likely to result in the greatest (98% probability) VE risk reductions compared to alendronate, risedronate and ibandronate treatments. Recently, by a new Bayesian meta-analysis[42] the same Author confirmed that there is a 79% probability that zoledronic acid shows the greatest reduction in VE compared to alendronate, ibandronate, risedronate, and etidronate.

These nine studies included placebo controlled trials having new VF as primary endpoint; since no head-to-head evidence was available for any considered antireabsorptive agent. Calcium in-

take was different between trials regarding zolendronate risedronate and denosumab (1000-1500 mg/daily) and trials about alendronate and ibandronate (500 mg/daily); also Vitamin D intake was different between Trials on zolendronate and denosumab (1200-800 UI/daily) and trials on risedronate (0-500 UI/daily) or alendronate (250 UI/daily) and ibandronate (400 UI/daily). Percentage of prevalent VE was strongly different among RCT. In the Freedom study, only 23% of patients treated with denosumab had one or more vertebral fracture at baseline, while in the horizon study the percentage of prevalent VE was 62% and in the VERT trials was respectively 100% and 80%, in the Bone study 94% and in the FIT 2 only 24% (see Table II). These differences may be taken into account when interpreting results of the mixed comparison treatment.

One of the limitations of this study is the lack of possibility to accomplish a randomized effect model MTC, due to exiguity of the sample. As a matter of fact in order to consider unknown differences of covariates that act as effect across trials, a random effect approach should be brought about to capture the possibility of the presence of heterogeneity across comparisons. It has been possible to use only a fixed effect model in this MTC.

Furthermore, only alendronate, risedronate, ibandronate, zolendronate and denosumab are considered. There are a number of additional compounds for antiosteoporotic treatment that were not included in the analysis (clodronate, etidronate, anabolic agent, strontium ranelate). The main reason for focusing on these five antireabsorptive agents is that they are the most widely used in clinical practice. Moreover anabolic agents are indicated for severe OP and strontium ranelate given its own mechanism of action, antireabsorptive and also anabolic, can not be considered as an antireabsorptive drug.

Results showed that zolendronate and denosumab had the highest probability to be the most effective treatment; these results have to be analyzed considering several clinical issues.

Although efficacy is an important element influencing the choice on OP treatment other factors are also important, such as, safety and compliance[43]. Since compliance to anti-osteoporosis treatment is poor, consequently efficacy in real clinical practice is lower than expected from RTC with consequent major expenditure[44]. Among the bisphosphonates, significant differences about compliance to treatment were observed between the various treatment regimens,

being highest for monthly and lowest for daily regimens[45]. This lack of compliance to medication has serious consequences on osteoporotic patients resulting in a significantly higher fracture risk. On the contrary, since zoledronate is given by a yearly intravenous route, it developed an increased compliance by overcoming the frequent and burdensome dosing requirements of oral bisphosphonates[46].

Recently, Kendler et al[47] reported a significantly greater adherence to treatment in patients treated with subcutaneous denosumab every six months than those treated with oral alendronate once weekly.

Obviously dosing regimen is only one of the elements influencing the adherence to osteoporosis treatment; lack of motivations, doubts about long term safety, side effects, tolerableness, costs, lack of efficacy have a relevant impact in the determination of poor adherence to OP therapy[48].

One of the more relevant issues is safety. The most common adverse events (AEs) observed with zoledronate (ZOL) in OP are acute-phase reactions, usually characterized by flu-like symptoms, headache, pyrexia, arthralgia, and myalgia. Most of these symptoms occur within the first 3 days after infusion and usually decrease within several days after administration The incidence of asymptomatic and transient hypocalcemia with ZOL has been reported in some reports; generally, the renal effects were short term, mild, and transient[49,50].

Individual studies of ZOL have found an increased incidence of atrial fibrillation (AF); however, larger epidemiological studies have found no increased risk of AF in patients receiving bisphosphonate treatment. In the HORIZON-RFT study, which included an older patient population with more comorbidities compared with other osteoporosis trials, the incidence of serious AF was similar with ZOL and placebo (1.0% ZOL vs 1.2% placebo)[17,18].

The safety data from the HORIZON-PFT study showed that of the 7,714 patients in the study, there were only 2 cases of possible osteonecrosis of the jaw (ONJ): one in a patient receiving ZOL and other in a patient receiving placebo. In several other studies with ZOL for the treatment of osteoporosis and Paget's disease, no cases of ONJ were reported[51,52].

Overall, the incidence of ONJ in osteoporotic patients receiving ZOL is very low, and this can be managed with no special treatment beyond routine dental care.

The incidence of ONJ in patients using oral biphosphonates (BPs) for osteoporosis is low, and associated with other risk factors for development of ONJ, such as infection, lack of personal hygiene, cancer, immunodepression due to drugs and\or morbidities[53,54]. Up until now, ONJ has not been reported in the clinical trials with denosumab.

Regarding denosumab, AEs and serious AEs (SAEs) were similar in character and percentage with denosumab compared with placebo[55] On the contrary Anastasilakis et al analyzing data from nine RCTs involving 10 329 participants, reported an increased risk of serious adverse events [OR (95% CI) 1.83 (1.10 to 3.04), $p = 0.02$] and serious infections [OR (95% CI) 4.45 (1.15 to 17.14), $p = 0.03$], concluding that its increased infection risk questions its safety[56].

With regard to oral BPs, gastroesophageal safety is one of the hardest problems in clinical practice. RCTs on bisphosphonates showed similar data about safety of upper GI tract between active drug and placebo. However, postmarketing studies have indicated that oral bisphosphonates can be associated with GI tract intolerance[57,58].

Head to head studies showed a better tolerance to risedronate than alendronate[59].

Conclusions

The results of this MTC may be relevant for clinical physicians and health care management decision-making, suggesting a rank of interventions among available antireabsorptive agents.

It might be relevant also from a social point of view, given the burden of OP fragility vertebral fractures affecting aging populations in western countries.

Although the mixed treatment comparisons among alendronate, risedronate, ibandronate, zolendronate and denosumab did not show a statistically significant difference, this analysis suggests that Zolendronate, compared to placebo, is expected to provide the highest rate of reduction in VF affecting OP patients.

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