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Review Article

Systematic Literature Review of Biphosphonates and Osteonecrosis of the Jaw in Patients With Osteoporosis☆

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ABSTRACT

Objective: To systematically assess the literature related to the occurrence of osteonecrosis of the jaw (ONJ) using bisphosphonates (BP) in the treatment of osteoporosis (OP).
Methods: We conducted a systematic literature search in PubMed, EMBASE and the Cochrane Central Register of Controlled Trials up to July 2010, including terms relating to OP, ONJ, and BP (MeSH and free text). We selected meta-analysis, systematic reviews (SRs) and clinical trials (CTs), English or Spanish, including patients >18 years of both sexes with OP treated with BP (intravenous and oral). Furthermore, studies should evaluate the occurrence of ONJ during treatment with BP. We excluded studies that included patients with cancer or diseases other than OP, animal studies and basic science. The selection of articles both by title and 2 independent reviewers conducted a detailed review of the abstracts. We used the modified Oxford Scale (version 2001) to assess the quality of the included studies.
Results: We identified 1422 articles of which we included 18 (8 SRs, 8 CT and 2 meta-analysis). Most studies were of good quality and examined the use of BP in middle-aged women with OP. Frequency of ONJ was low.
Conclusions: We found insufficient evidence to affirm that intravenous or oral BP used exclusively for the treatment of OP lead to a significant risk of ONJ (evidence level 2a, grade B recommendation).

Revisión sistemática de la literatura sobre la osteonecrosis maxilar con el uso de bisfosfonatos en pacientes con osteoporosis

Palabras clave:
Osteonecrosis de mandíbula
Bisfosfonatos
Osteoporosis

RESUMEN

Objetivo: Evaluar sistemáticamente la literatura en relación con la aparición de osteonecrosis de mandíbula (ONM) con el uso de bisfosfonatos (BF) en el tratamiento de la osteoporosis (OP).
Métodos: Se realizó una búsqueda sistemática de la literatura en *Pubmed*, *EMBASE* y la *Cochrane Central Register of Controlled Trials* hasta julio de 2010 incluyendo términos relativos a OP, ONM, y BF (mesh y texto libre). Se seleccionaron metaanálisis, revisiones sistemáticas y ensayos clínicos (EC), en inglés o español, que incluían pacientes > 18 años de ambos sexos con OP en tratamiento con BF (por vías intravenosa y oral). Además, los estudios debían evaluar la aparición de ONM durante el tratamiento con BF. Se excluyeron los estudios que incluían pacientes con cáncer u otra enfermedad distinta de la OP, estudios en animales y ciencia básica. La selección de los artículos, tanto por título y abstract como la revisión en detalle, la realizaron 2 revisores de forma independiente. Se utilizó la escala de Oxford modificada (versión del 2001) para evaluar la calidad de los estudios incluidos.
Resultados: Se identificaron 1.422 artículos, de los que se incluyeron 18 (8 revisiones sistemáticas, 8 EC y 2 metaanálisis). La mayoría de los estudios son de buena calidad y estudiaron el uso de BF en mujeres de mediana edad con OP. La frecuencia de ONM fue baja.

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Conclusiones: No hemos encontrado evidencia suficiente para afirmar que los BF por vía oral ni intravenosa utilizados exclusivamente para el tratamiento de la OP confieran un riesgo significativo de ONM al paciente (nivel de evidencia 2a, grado de recomendación B).

Introduction

OP is a disease characterized by decreased bone strength, predisposing an increased risk of fracture.[1] Its prevalence increases with age and is a serious public health problem because it can potentially cause devastating results and has a high cumulative rate of fractures. It is estimated that up to 50% of Caucasian women (and 20% of men) over age 50 will have an osteoporotic fracture over their lifespan.[2–4] The most relevant fractures are vertebral, forearm and especially the hip. They produce functional impairment and increased morbidity, as well as an increased use of health resources.

Randomized clinical trials (RCTs) have shown that BP increase bone mineral density and reduce the risk of fractures.[5,6] Nitrogenated BPs (alendronate, risedronate, ibandronate, pamidronate and zoledronate) are the first therapeutic option for the management of OP. BPs are inorganic pyrophosphate analogs, which are not metabolized to the hydroxyapatite found in bone and remain there for 10–12 years,[7,8] and are released in very small quantities during bone remodeling. They inhibit osteoclastic bone resorption by inhibiting farnesyl diphosphate synthetase. Their antiresorptive potency and retention in bone differ depending on the BP.

Moreover, in 2003 the first clinical case of ONJ in a patient treated with BP was published. Since then, there have been over 2400 cases[9] generally in cancer patients treated with intravenous BP. Based on case reports or case series, the incidence of ONJ associated with intravenous BP in patients with cancer has been estimated between 1% and 10%.[10] The lack of agreement in the estimates of incidence is attributed to differences in methodology when identifying cases and difficulties in accurately quantifying the patients treated with BP. There have also been some cases of ONJ in BP treated OP patients, but the true incidence is unknown. Estimates range from less than 1/100 000 to over[10] 1/10 000 cases-year.

We designed this study to estimate the incidence of ONJ in patients diagnosed with OP treated with BP.

Materials and Methods

We conducted a SR of the scientific literature aimed at estimating the incidence of ONJ in BP treated OP patients.

Search Strategy

Studies were identified through a literature search of major databases. For this purpose, an expert documentarian worked and verified them. The terms used to capture and the results are shown in Table I (available in the electronic version of this article). The following databases were screened: Medline (from 1996 to July 20, 2010), EMBASE (1991 to July 20, 2010) and Cochrane Central. We also searched the abstracts of the EULAR and ACR congresses of the years 2008, 2009 and 2010. There were no language restrictions. All references retrieved were handled in EndNote X3 (Thomson Reuters). Finally, a manual search was conducted by reviewing the references of studies included.

Selection Criteria for Studies

The studies retrieved by the above search strategy were included if they met the following inclusion criteria. Patients had to be ≥18 years with OP of non-malignant etiology and treatment for OP with one of the BP (alendronate, etidronate disodium, ibandronic acid, pamidronate, risedronate and zoledronic acid) or strontium ranelate. We included meta-analyzes, SRs and CT. The comparator group in the RCT could be placebo or active drug. It should analyze the presence of ONJ as a measure of outcome. We excluded animal and basic science studies.

Study Selection, Data Collection and Analysis

Two reviewers independently examined the titles and abstracts of the articles retrieved with the selection criteria. This process was conducted in 20 min sessions. The 2 reviewers extracted the data from studies included using ad hoc standardized forms. All items collected were double and independent. One reviewer entered data forms into a spreadsheets. If, in doing so, the reviewer noticed a discrepancy between the information and the other reviewer, then a consensus was reached by reviewing the original article or by asking a mentor. Items which did not meet all the inclusion criteria or had insufficient data were excluded. To classify quality, we used a modification of the Oxford Centre for Evidence-based Medicine Levels of Evidence[11] in which the levels of evidence correspond to: (1a) SR of RCTs with homogeneity, i.e. including studies with comparable results and the same objectives; (1b) individual RCT (with narrow confidence intervals); (1c) proven through clinical practice rather than experimentation; (2a) SR of cohort studies with homogeneity and (2b) individual cohort randomized clinical trials of low quality (<80% follow up); (2c) research studies and ecological "Results"; (3a) case–control studies with homogeneity; (3b) individual studies of cases and controls; (4) case-cohort and low-quality case–control series; (5) expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles". Evidence tables were constructed. The meta-analysis was planned just in case there was sufficient homogeneity between the studies included.

Results

We identified a total of 1422 articles, of which we finally included 18 (Fig. 1). In Table II we show excluded studies and

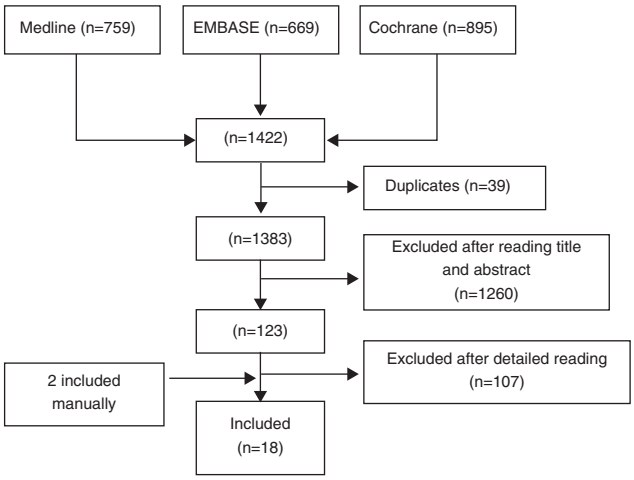

Fig. 1. Article flow chart.