ORIGINAL ARTICLE

Assessing the risk of osteonecrosis of the jaw due to bisphosphonate therapy in the secondary prevention of osteoporotic fractures

**F. Lapi · F. Cipriani · A. P. Caputi · G. Corrao ·
A. Vaccheri · M. C. Sturkenboom · M. Di Bari ·
D. Gregori · F. Carle · T. Staniscia · A. Vestri ·
M. Brandi · V. Fusco · G. Campisi · G. Mazzaglia ·
on behalf of the Bisphosphonates Efficacy-Safety Trade-
off (BEST) study group**

Abstract

Summary There is evidence that the use oral bisphospho-nates can lead to osteronecrosis of the jaws (ONJ). Although the occurrence of ONJ appears rare among oral bisphosph-onates (BPs) users, it is important to know that it exists and can be opportunely minimized.

F. Lapi · F. Cipriani · G. Mazzaglia
Regional Agency for Healthcare Services of Tuscany,
Florence, Italy

F. Lapi
Department of Preclinical and Clinical Pharmacology,
University of Florence,
Florence, Italy

F. Lapi
Centre for Clinical Epidemiology,
Jewish General Hospital,
McGill University,
Montreal, QC, Canada

A. P. Caputi
Department of Medicine and Pharmacology,
University of Messina,
Messina, Italy

G. Corrao
Unit of Biostatistics and Epidemiology, Department of Statistics,
University of Milan-Bicocca,
Milan, Italy

A. Vaccheri
Department of Pharmacology, University of Bologna,
Bologna, Italy

M. C. Sturkenboom · G. Mazzaglia
Department of Medical Informatics, Pharmacoepidemiology Unit,
Erasmus University Medical Center,
Rotterdam, The Netherlands

M. Di Bari
Department of Critical Care Medicine and Surgery,
Unit of Gerontology and Geriatrics, University of Florence,
Florence, Italy

D. Gregori
Department of Public Health and Environmental Medicine,
University of Padua,
Padua, Italy

F. Carle
Center of Epidemiology, Biostatistics, and Medical Information
Technology, Polytechnic University of Marche,
Ancona, Italy

T. Staniscia
Department of Medicine and Aging, University "G. d'Annunzio",
Chieti-Pescara, Italy

A. Vestri
Department of Public Health and Infectious Disease,
University "La Sapienza",
Rome, Italy

M. Brandi
Department of Internal Medicine, University of Florence,
Florence, Italy

V. Fusco
Oncology Unit, Alessandria Hospital,
Alessandria, Italy

Introduction The purpose of this study is to evaluate the association between BPs prescribed for the secondary prevention of osteoporotic fractures and the occurrence of ONJ. *Methods* An Italian record linkage claims database with a target population of around 18 million individuals (6 million over 55 years of age) constituted the data source. We conducted a nested case–control study within a cohort of individuals aged 55+years old, who were discharged from hospitals with a primary diagnosis of incident osteoporotic fracture. The date related to the discharge diagnosis of ONJ was the index date. Conditional logistic regression for matched data was fitted to estimate the odds ratio (OR) along with 95 % confidence intervals (95 % CI) for the likely association between use of BPs and the risk of ONJ. *Results* Any one of the 61 ascertained cases of ONJ (incidence rate, 36.6 per 100,000 person-years) was matched to 20 controls for a total of 1120 controls. When the exposure to BPs was modeled according to recency (i.e., exposure time window prior to the index date) of use, the adjusted OR (95 % CI) for current users was 2.8 (1.3–5.9) against never users. The cumulative use of BPs has shown to increase the incidence of ONJ among patients with primary osteoporotic fractures, although not statistically significant risk has been observed. *Conclusions* Although the risk of BP-related ONJ appears low in non-oncological indications, it is important to be aware that it exists and to know how it may be predicted and possibly minimized.

Keywords Bisphosphonates · Nested case–control study · Osteonecrosis of the jaw · Osteoporotic fractures

Introduction

Osteonecrosis of the jaw (ONJ), a rare condition characterized by exposed necrotic bone in the maxillofacial region [1, 2], has received increasing attention since case reports among patients exposed to bisphosphonates (BPs) were published in 2003 [3, 4].

The ONJ clinical picture mainly consists of non-healing ulcerated oral lesions and visible necrotic bone, which are sometimes associated with a diffuse jaw or facial pain [2, 5–7]. The exact etiologic mechanisms remain unclear, but it might relate, in part, to altered bone remodeling or local tissue effects in susceptible patients [1, 8, 9].

Most affected patients have incurred ONJ after invasive dental procedures that involved dental bone manipulation, although spontaneous exposure of bone has been also observed. Cofactors have not been firmly established, although smoking, steroid use, anemia, hypoxemia, diabetes, infections, and immune deficiency may be important [2, 5–7]. Indeed, as only a minority of BPs users develop ONJ, it is conceivable that individual pharmacokinetic and pharmacodynamic genetic variations may confer susceptibility or resistance in developing this complication. Among genetic determinants, polymorphisms on *CYP2C8* gene [10] and of *FDPcS* gene [11] arise as promising risk factors.

To date, most of the reported cases have been related to zoledronic or pamidronic acid when they were administered intravenously to control metastatic bone disease or multiple myeloma [4, 12, 13], for which reported ONJ incidence ranges from 4 to 10 %, and the mean time of onset varies from 1 to 3 years [1, 14, 15].

Early case series also identified approximately 5 % of the reported cases occurring in patients receiving oral BPs [1, 8], primarily used for the prevention of osteoporotic fractures. However, limited data exist about the ONJ risk with such medications, and most of the published evidence are derived from surveillance data [16]. A study from Germany, which used information from the Central Registry of ONJ, reported a prevalence among patients treated with BPs for osteoporosis of 0.00038 % [17]. In a survey of 8572 Kaiser Permanente respondents, the prevalence of ONJ in patients receiving long-term (more than 2 years) oral BP therapy ranged from 0.05 to 0.21 %, depending on the duration of exposure [18]. Finally, in a nationwide survey of oral and maxillofacial surgeons in Australia, the incidence of ONJ among osteoporotic patient treated weekly with alendronate was 0.01–0.04 %. Following dental extractions, this rate increased to 0.09–0.34 % [14]. In addition, inferences from observational epidemiologic studies published so far offer conflicting results, and in most of the cases, they are subjected to unmeasured confounding and biases [19–21].

Given the increasing number of persons taking oral BPs for the treatment of osteopenia/osteoporosis [22], it is important to accurately determine the incidence of ONJ using rigorous case ascertainment criteria and to assess the risk associated with long-term use of such medications. We therefore conducted a nested case–control study to evaluate the possible association between the use of oral BPs prescribed for the secondary prevention of osteoporotic fractures and the occurrence of ONJ.

G. Campisi
Department of Surgical and Oncological Disciplines,
Sector of Oral Medicine, University of Palermo,
Palermo, Italy

F. Lapi (✉)
Department of Preclinical and Clinical Pharmacology,
University of Florence (Italy),
Viale G. Pieraccini 6,
50139 Florence, Italy
e-mail: francesco.lapi@unifi.it

Methods

Data source

The data used for this study were obtained from the *Bisphosphonates Effectiveness Safety Trade-off* (BEST) network. It collects record linkage encrypted information on patient demographics, hospital discharge schemes (HDS), the related surgical and/or diagnostic procedures [since January 1, 1998 to December 31, 2007; coded by *International Classification Disease, 9th version, Clinical Modification* (ICD9CM)], any reimbursed drug prescription (since January 1, 2003 to December 31, 2007; coded by Anatomical Therapeutic Chemical classification), and the mortality registers (since January 1, 2003 to December 31, 2007) from a target population of around 18 million people residing in four Italian Regions and in the catchments areas of ten Local Health Authorities (LHA). The study was approved by the Local Research Ethics Committees of each Region or LHA being involved into the project.

Cohort selection

The process of cohort selection is depicted in Fig. 1. All patients aged 55+years, who were discharged because of an osteoporotic fracture during the period July 1, 2003–December 31, 2005, were identified. Fractures were selected among ICD9CM codes (primary and secondary positions) consistently associated to osteoporotic fractures site, (23–27) such as vertebrae (codes: 733.13, 805*), pelvis (code: 808*), femur/hip (codes: 733.14, 820*, 821*), and tibia/fibula (codes: 733.16, 823*) [23–26]. The date of the first recorded HDS of osteoporotic fracture was considered as the "entry date" of follow-up.

Patients were excluded if they had, before the entry date, less than 6 months of tracking period, an evidence of hospitalization for osteoporotic fracture or fractures at multiple sites (i.e., more likely to be associated with non-osteoporotic fracture), Paget's disease (code: 731*), and malignant neoplasms (codes: 140 to 208). The prescription of BPs in the 6 months prior to entry date has been also considered an exclusion criterion. No cases of ONJ (see "Cases and controls definition" section) were captured before the entry date.

Each participant accrued person-years of follow-up from the entry date until the earliest of the following events: ONJ-related diagnosis, occurrence of one of the exclusion criteria (with the exception of osteoporotic fractures), death, transferring out of BEST catchment areas, or end of the study period (December 31, 2007).

Cases and controls definition

Cases were members of the study cohort who had experienced an ONJ event during the follow-up. Since there were no specific ICD9CM codes for the ONJ-related events during the study period, a four-step process identified ONJ cases from the study population.

First, potential ONJ cases have been retrieved for main or secondary diagnosis from ICD9CM and Current Procedural Terminology billing codes from the regional or LHA registries of the HDS. In a preliminary evaluation, a highly sensitive case-finding procedure has been implemented. Subsequently, an adjudication committee composed by a panel of experts in dentistry, oncology, geriatric, and pharmacology selected from the preliminary list only diagnostic codes and procedures that could have been most likely used to describe or treat a necrotic lesion of the jaw. Second, among the selected cases, additional information was collected from the medical charts using a structured questionnaire. The questionnaire included information on descriptive discharge diagnosis, tomography or panoramic imaging, history of dental extraction, tissue biopsy, signs or symptoms. Third, the collected questionnaires were reviewed by the study staff for excluding potential false positives (i.e., patients with direct or indirect evidence of cancer, trauma, osteonecrosis at other bone sites as well as signs and/or symptoms related to the main other oral–maxillary diseases). Fourth, remaining cases were classified by two ONJ experts as "definite" (i.e., 22 cases) if: (1) sign or symptoms suggesting necrotic bone lesions, inflammatory jaw condition not related to strict dental causes, and open lesions/ulcers of the jaw were recorded. All lesions related to soft tissues (e.g., recurrent aphthous ulcers) were purposely identified and excluded; [5] (2) the ONJ was specifically mentioned in the medical chart; and (3) pain was not directly referred to dental extraction or other surgical procedures. The other cases not fulfilling these criteria were classified as "probable" (i.e., 39 cases). For each case, up to 20 controls were randomly selected among the patients' cohort. Controls were matched to their respective case by sex, age (±3 years), month, and year of the cohort entry. The date of ONJ-related diagnosis was the "index date," and the same date was assigned as the index date to the respective matched controls.

Exposure assessment

Patients have been considered on BPs treatment once they received a prescription between the entry date and the index date. The number of days supplied from each prescription has been calculated assuming a standard dosing regimen, as assessed by the defined daily dose. It has also been used to calculate the sum of days of BPs exposure (plus 28 days to account for potential hospital prescriptions) during the entire follow-up. For each patient, adherence to BPs was therefore estimated by dividing the sum of days of BPs exposure with the follow-up [medical possession ratio (MPR)], and
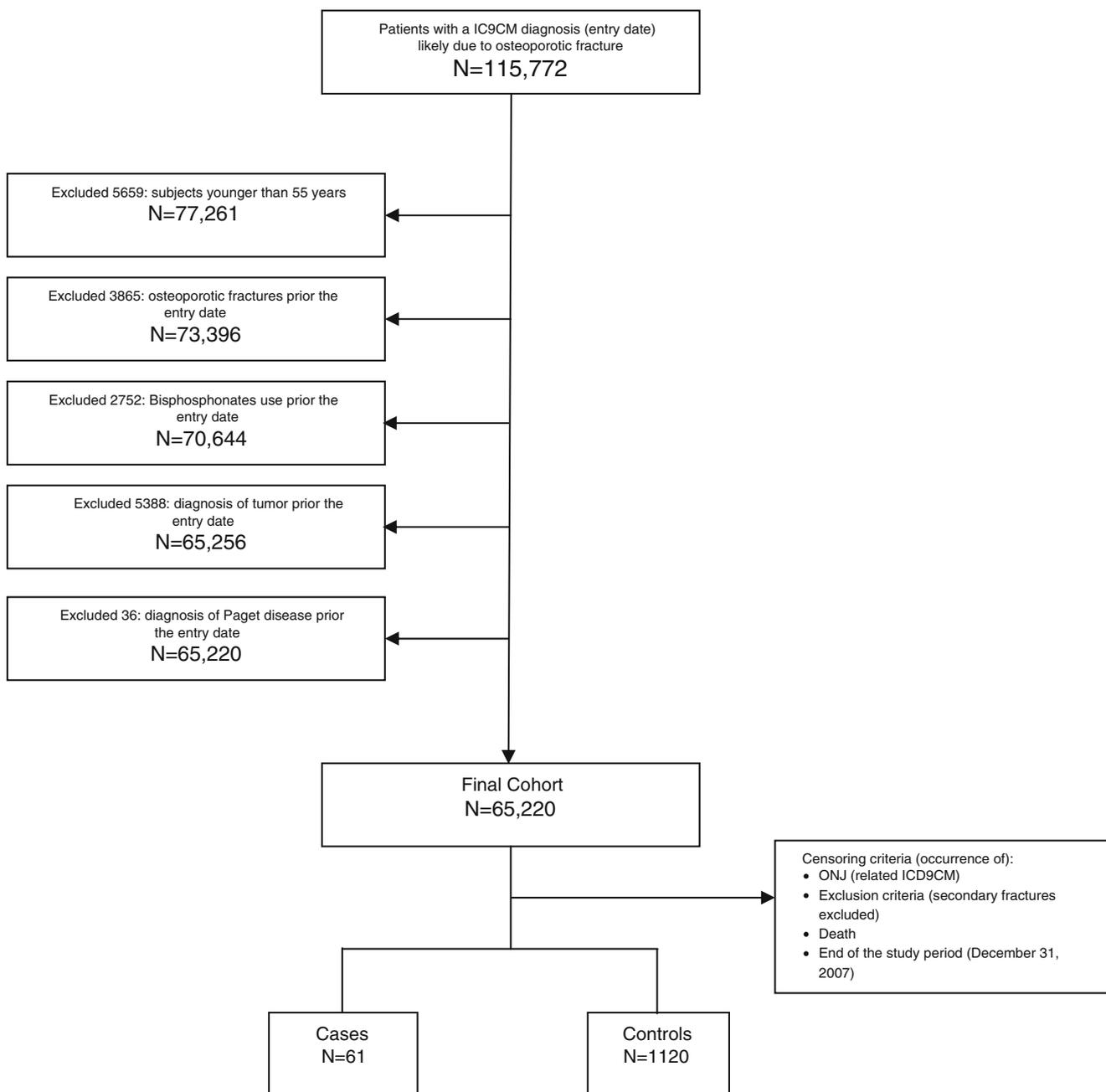
Fig. 1 Flow chart of cohort and case–control selection process

further classified into the following adherence levels: high (MPR ≥80 %), intermediate (MPR=40–79 %), and low (MPR <40 %).

Following the case and control selection, patients were categorized into mutually exclusive categories of current use, past use, and non-use, according to latest date of BPs pharmacy claims supply before the index date. Current use has been defined as latest date of exposure occurring within 1 year before the index date; past use as exposure interrupted more than 1 year before the index date, and non-use as no recorded BPs prescription at any time during follow-up.

Current users have been further subdivided into four categories (i.e., ≤90 days, from 91 to 179 days, from 180 to 364 days, and ≥365 days) according to the sum of days of BPs exposure during follow-up.

Covariates

As covariates, we evaluated the patients' demographics (i.e., age and gender) and the presence of risk factors for ONJ as commonly described in the most recent guidelines on ONJ [5, 7]: (1) concurrent drug use [i.e., antithrombotics, proton

pump inhibitors (PPIs), non steroidal anti-inflammatory drugs (NSAIDs), beta-blockers, antidepressants, antiepileptic drugs, lipid-lowering drugs, calcium and/or vitamin D supplements, immunosuppressant, and corticosteroids; captured within 1 year before the index date]; (2) concurrent diseases (captured any time before the index date), such as diabetes mellitus (code 250* and use of antidiabetic drugs), vascular coagulation disorders (codes 093.0, 286*, 287.1, 287.3 through 287.5, 440*, 441*, 443.1 through 443.9, 447.1, V43.4), and the Charlson Comorbidity Index (CCI) as index of chronic severity degree. Occurrence of any osteoporotic fracture during follow-up was not censored, and it was considered in the case–control analysis.

Data analysis

Density method has been used in measuring the incidence of ONJ. The number of events that occurred during follow-up and the person-months cumulatively spent in the corresponding periods by the cohort members constituted the numerator and the denominator of the incidence rates, respectively.

Statistical differences between cases and controls were evaluated by means of χ^2 or t tests for categorical and continuous variables, respectively. Conditional logistic regression for matched data was fitted to estimate the odds ratio (OR) along with the corresponding 95 % confidence intervals (95 % CI), for the association between use of BPs and the risk of ONJ. After Mantel–Haenszel test, the OR estimates were adjusted for those variables significantly (10 %) affecting the crude relationship between BPs and ONJ.

To test the robustness of our findings, some sensitivity analyses were performed. Firstly, the analyses were restricted to definite cases only. Secondly, because the allocation of BPs therapy was not randomized and the indication for treatment may be related to the risk of future health outcomes, a propensity score (PS) matching design was carried out with the aim of taking into account the confounding by indication [27]. The PS was estimated at patient level by performing a multivariable logistic regression. Each known predictor of BPs exposure and ONJ occurrence, as well as those risk factors for ONJ constituted the covariates vector which established the propensity to BPs use. All variables were imputed in the model in a non-parsimonious way according to methodological literature [28]. Afterwards, cases and controls were matched (1:20) by the corresponding PS within ±0.1. Finally, to account for the possible effect dilution due to short-term BPs users, all models were rerun by excluding individuals who begun the therapy less than 6 months before the index date.

All analyses were performed using STATA 10.0 for Windows. Statistical significance was defined as a p value less than 0.05.

Results

From the BEST database, 115,772 patients with an HDS for osteoporotic fracture were selected between January 1, 2003 and December 31, 2005. Of these, 65,220 patients aged 55 years and older, after the application of the exclusion criteria, constituted the comprehensive study cohort (Fig. 1).

Incidence rates

During the follow-up, we identified 61 cases of ONJ (22 definite), with an incidence rate of 36.6 (95 % CI, 28.5–46.9) per 100,000 person-years. An increased incidence has been observed among patients with diabetes mellitus [77.3 (95 % CI, 46.6–128.4)], as well as among those being prescribed corticosteroids during follow-up [58.3 (95 % CI, 24.2–140.1)]. Higher incidence has been also reported among BPs users [46.0 (95 % CI, 24.8–85.5)], when compared with nonusers [35.2 (95 % CIs, 26.8–46.3)]. Among BPs users, we have also observed a growing trend related to the adherence levels, with incidence ranging from 27.3 (95 % CIs, 10.3–72.8) among low adherers (MPR<40 %) to 111.7 (95 % CIs, 27.9–446.6) among high adherers (MPR≥80 %).

Nested case–control study

All 65,220 eligible patients were followed up (median, 2.7 years), and 61 ONJ cases along with 1120 matched controls were considered for the analysis. The characteristics of the cases and controls at the index date are described in Table 1. Overall, cases were more likely to have comorbid conditions, as assessed by using the CCI, or by diabetes prevalence (27.9 vs. 17 %). They were also more likely to be prescribed with co-medications such as antithrombotics (50.8 vs. 30.5 %) and immunosuppressant (4.9 vs. 0.2 %). After adjustment for selected covariates, we observed a nonstatistically significant increased risk of ONJ (OR, 1.7; 95 % CI, 0.8–3.6) associated with BPs use. However, when the analysis was restricted to current users, a statistically significant 2.8-fold increased risk was reported (OR, 2.8; 95 % CI, 1.3–5.9), when compared to nonusers (Table 2). The statistical significance among current users was confirmed in a sensitivity analysis which selected propensity-matched controls (OR, 2.3; 95 % CI, 1.1–5.1).

Upon restriction to 22 definite ONJ cases and 440 matched controls, the association maintained similar risk among current users (OR, 2.5; 95 % CI, 0.7–9.5). In such analysis, also a longer exposure with oral BPs (i.e., 180–364 days) showed a clearer trend toward an increased risk of ONJ (OR, 4.2; 95 % CI, 0.5–41.4), although, due to the small sample size, it did not reach the statistical significance. Finally, the exclusion of individuals who started the therapy

Table 1 Characteristics of case and controls at the index date

	Cases		Controls		
	N=61	%	N=1120	%	p value
Gender, female	42	68.9	840	68.9	-
Age (mean±SD)	73.2±0.7		73.1±9.1		-
Comorbidity					
CCI					0.001
0	21	34.4	687	56.3	
1	22	36.1	299	24.5	
2	7	11.5	139	11.4	
3+	11	18.0	95	7.8	
Diabetes mellitus[a]	17	27.9	207	17.0	0.029
Osteoporotic fractures (secondary)	8	13.1	171	14.0	0.843
Vascular and coagulation disorders	6	9.8	30	2.5	0.001
Co-medications					
Antithrombotics	31	50.8	372	30.5	0.001
PPIs	14	23.0	194	15.9	0.145
NSAIDs	11	18.0	215	17.6	0.935
Beta-blockers	11	18.0	117	9.6	0.032
Antidepressants	10	16.4	171	14.0	0.603
Antiepileptic drugs	6	9.8	69	5.7	0.175
Lipid-lowering drugs	6	9.8	111	9.1	0.845
Calcium and/or vitamin D supplements	6	9.8	134	11.0	0.779
Immunosuppressant drugs	3	4.9	2	0.2	<0.001
Corticosteroids	2	3.3	77	6.3	0.337

SD standard deviation, *CCI* Charlson Comorbidity Index, *NSAIDs* non steroidal anti-inflammatory drugs, *PPIs* proton pump inhibitors

[a]ICD9CM coded diagnosis or an antidiabetic prescription

less than 6 months before the index date did not change the results (data not shown).

Discussion

To the best of our knowledge, this is the first investigation which estimated the risk of being exposed to oral BPs among a series of ascertained cases of ONJ. In specific, the exposure to BPs was 2.8-fold higher among patients who incurred ONJ when compared with their matched controls. In addition, although not statistically significant, a growing duration of BPs use showed an association trend toward an increased risk of ONJ occurrence.

In spite of numerous publications, very few evidence has been able to draw definite conclusions about the strength of

Table 2 Association between exposure to oral BPs and ONJ

	Cases N=61	Controls N=1220	Crude OR (95 % CI)	Adjusted OR[a] (95 % CI)
BPs use (any time)				
No	51 (83.6)	1102 (90.3)	Reference	Reference
Yes	10 (16.4)	118 (9.7)	1.9 (0.9–3.8)	1.7 (0.8–3.6)
BPs use (recency of use)[b]				
Past use	0	40 (3.3)	–	–
Current use	10 (16.4)	78 (6.4)	2.9 (1.3–6.0)	2.8 (1.3–5.9)
BP cumulative use (days)[c]				
≤90	4 (6.6)	49 (4.0)	1.8 (0.6–5.1)	1.8 (0.6–5.2)
91–179	2 (3.3)	25 (2.1)	1.8 (0.4–8.1)	1.7 (0.4–7.8)
180–364	2 (3.3)	22 (1.8)	2.0 (0.5–9.1)	1.9 (0.4–8.6)
≥365	2 (3.3)	22 (1.8)	2.0 (0.5–9.1)	2.0 (0.4–9.8)

[a]Adjusted for diabetes, corticosteroids, PPIs

[b]Current use: the latest date of exposure to BPs occurring within 1 year before the index date; past use: exposure to BPs interrupted more than 1 year before the index date

[c]Cumulative use was assessed from the start date until the index date among current users

the association between ONJ and oral BPs, in particular when they are prescribed for preventing osteoporotic fractures. Zavras et al. [19], analyzing medical claims from approximately 20 million people in the USA, reported a fourfold increased risk of jaw surgery associated with intravenous BPs, and a nonsignificantly increased association with oral BPs. Pazianas et al. [20] used jaw surgery as a surrogate marker for ONJ and did not find any association with oral BPs. Etminan et al. [29] reported a significant relative risk of 2.87, 2.43, and 3.34 of any-site aseptic osteonecrosis for alendronate, etidronate, and risedronate, respectively. Nevertheless, none of the mentioned studies formally validated the outcome, thus making difficult to provide definite explanations to their findings.

More recently, a case–control study [21] enrolling 191 validated ONJ cases and 573 controls in 119 dental practices reported a strong association (OR=12.2; 95 % CIs, 4.3–35.0) between oral BPs and ONJ. However, this study included cancer patients, thus increasing the potential for residual confounding. A second limitation concerned the fact that information about medication use was obtained from telephone interviews. In these conditions, the likelihood for a recall bias could be substantial because of the high proportion of false negatives among controls, which could result in a potential overestimation of the risk [30].

In our study, we addressed these potential biases by excluding and censoring from the selected cohort patients with cancer who could be exposed to chemotherapy and/or parenteral BPs. Because of the short time window available before the "entry date" and the likelihood of underdetection of anticancer therapy issued at hospital level, we have also used very restrictive criteria for excluding the potential remaining cancer-related ONJ cases in the formal validation of medical charts. For what concerns the exposure, because it was assessed from pharmacy records, which could be regarded as a virtually complete source of information, recall bias was unlikely to occur.

Osteonecrosis of the jaw has been also associated with duration of BPs treatment, with an estimated range of 1.6 to 4.7 years, depending on BPs type [1]. However, for non-cancer patients (the vast majority of whom take oral BPs), the ONJ risk seems to increase substantially after 5 years [21]. In our study, we have found a statistically significant association even after a median follow-up of 2.7 years, with cumulative BP use shorter than expected. Selective prescribing was unlikely to occur since sensitivity analyses made with propensity-matched controls showed results similar to the main analysis. Therefore, such findings might be partially explained by the inclusion into the cohort of greater-risk patients, specifically those discharged with an osteoporotic fracture.

This association is also supported by a biological rationale. Bisphosphonates affect the physiological bone remodeling by inducing an inhibition of osteoclast recruitment, decreasing osteoclast activity, and promoting osteoclast apoptosis. This process is exerted by inhibition of the mevalonate and cholesterol biosynthetic pathways, thereby reducing the production of lipids essential for protein prenylation or posttranslational modification of the guanine triphosphates (GTP) signaling which modulates the cellular apoptosis. When GTP is uncontrolled, the osteoclast can be disrupted by an irregular cytoskeletal rearrangement, membrane ruffling, and intracellular vesicle transport [31–33]. In this way, the long-term use of nitrogen-containing BPs leads to the development of abnormal osteoclasts which degenerate into necrotic bone tissue. Moreover, BPs can exert a direct inhibitory effect on cellular proliferation and angiogenesis in the healing of alveolar bone after dental extraction [34].

Our study has several noteworthy limitations. First, although the present findings consistently support the hypothesis of a duration–response relationship, the small sample size, besides the lower than expected proportion of ONJ patients exposed to oral BPs (10/61), did not allow us to provide robust estimates about the effect of cumulative BPs use. Second, we acknowledge the possibility of residual false positives among validated cases, especially those cases with inflammatory and suppurative jaw conditions, but without any additional registered sign or symptom suggesting necrotic bone lesions or open wounds/ulcers. However, in our cohort, ONJ incidence among BPs users was 46.0 (95 % CI, 24.8.1–85.5) per 100,000 person-years, higher than 1/10,000–1/100,000 range based on surveillance data [7, 17], but in agreement with two surveys conducted in Australia [14] and in the USA [18], which reported rates among patient exposed with oral BPs from 0.01 to 0.21 %. Furthermore, although the smaller number of cases did not permit to reach the statistical significance, the results from the sensitivity analysis conducted using only "definite" cases still indicated an increased risk among oral BP users, with a more evident cumulative effect of BPs. Thirdly, by assuming that patients who initiated the therapy had to be exposed at least 6 months to develop the ONJ, those with less than 6 months before the index date could have diluted the effect size. However, their exclusion from the analysis yielded similar results. Fourthly, the fact that ONJ was known as a BP-related disease could have introduced a detection bias among the exposed patients. Finally, some unmeasured confounders such as alcohol and smoking could have partly explained the association between the exposure and the outcome. Nevertheless, the presence of a duration-dependent association should overcome these two shortcomings.

From a clinical viewpoint, it cannot be denied that these medications have a demonstrated efficacy. In clinical trials, they have been associated with a reduction of incidence of

fractures related to postmenopausal osteoporosis by 20 to 45 % [35]. Several studies, conducted with claims databases in a "real-world setting," confirmed that greater adherence to BPs was significantly associated with a relative risk reduction of fractures after 24 months of follow-up ranging from 7 to 20 % [36]. Nevertheless, although the risk of BP-related ONJ is low in non-oncological indications, it is important to be aware that it exists and to know how this clinical issue may be predicted and possibly minimized.

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