BRONJ IN PATIENTS WITH RHEUMATOID ARTHRITIS: A MULTICENTRE CASE SERIES

Authors

Olga Di Fede[1], Alberto Bedogni[2], Francesco Giancola[1], Giorgia Saia[2], Giordana Bettini[2], Francesca Toia[1], Natale D'Alessandro[3], Alberto Firenze[4], Domenica Matranga[4], Stefano Fedele[5], Giuseppina Campisi[1]

Affiliations

[1]Department of Surgical, Oncological and Oral Sciences, University of Palermo, Via del Vespro 129, Palermo, Italy.
[2]Department of Neurosciences NPSRR, University of Padua, Via Giustiniani 2, 35100 Padua , Italy.
[3]Clinical Pharmacology Unit, Azienda Ospedaliera Universitaria Policlinico "P. Giaccone", Via del Vespro 129, Palermo, Italy.
[4]Department of Sciences for Health Promotion and Mother and Child Care "G. D'Alessandro", University of Palermo, Via del Vespro 129, Palermo, Italy.
[5]University College London, UCL Eastman Dental Institute, 256 Grays Inn Rd, London WC1X 8LD, United Kingdom.

Correspondence to: Olga Di Fede
Via del Vespro 129 90127 Palermo, Italy
odifede@odonto.unipa.it
phone - fax 0039 091 6552296

Abstract

Osteonecrosis of the jaw (ONJ), a potentially severe adverse effect of various medications (bisphosphonates, antiresorptive and antiangiogenic drugs). has unclear pathogenesis although some risk factors have been recognized. This observational study will describe a multicenter, case series of patients affected with RA (a potential risk factor) and ONJ, and it will attempt to evaluate the association between features of ONJ and pharmacological, systemic and site variables.

Demographic, pharmacological and clinical data from 18 RA patients with ONJ were collected and registered from three Italian centres (i.e. Palermo, Verona, Padua) from 2004 to 2013.

Sixteen(88.9%) patients were in therapy for RA: 9/18 (50.0%) with systemic steroids, 3/18 (16.7%) with methotrexate, and 4/16(22.2%) with both drugs. Two patients were not receiving treatment for RA. All patients took NBPs for secondary osteoporosis (average duration of 69 months, range 20-130): fifteen (83.3%) patients were treated with single NBPs, while 3/18(16.7%) with different molecules; one patient was also treated with denosumab. Mandible was affected more frequently (66.7%) than maxilla (33.3%); one patient presented multiple ONJ events.

This is the first multicenter case series in the international literature. It could be hypothesized that RA patients may be more susceptible to ONJ than the majority of osteometabolic patients.

Keywords. Rheumatoid Arthritis, Osteoporosis, Bisphosphonate, Denosumab, Jaw, Osteonecrosis, ONJ.

INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic, inflammatory, autoimmune disorder, characterized by progressive joint destruction and various systemic manifestations (e.g. hematological, neurological, respiratory, and cardiovascular events). RA is more frequent in women with a prevalence of about 1%, thereby suggesting a role for sex hormones. The annual incidence rate of RA varies between 20 and 50 cases per 100,000 in North American and north European countries, and it may be lower in south European countries (Alamanos et al., 2006, Carbonell et al., 2008); unfortunately, incidence studies from other countries are not currently available. RA is the most common form of inflammatory arthritis with the highest propensity to overstep in cases of synovitis, infiltrating articular bone and cartilage. Three types of alterations in bone mass can be recognized in RA patients: periarticular bone loss, joint erosions and generalized bone loss. Key drugs in the therapeutic regimens of RA are glucocorticoids (GCs), which have demonstrated a slowing of radiographic progression(Jacobs et al., 2014). Furthermore, the prescribing of Disease Modifying Anti-Rheumatic Drugs (DMARDs), such as metotrexate (MTX), is another essential regimen for RA therapy and is widely used(Dimitroulas et al., 2013). The event of generalized bone loss is a secondary osteoporotic condition, and it can be frequently aggravated by: (a) therapy with GCs and/or MTX (Salute), commonly used to treat RA; (b) physical inactivity (Vasquez et al., 2013), typically due to RA pain; and (c) inflammatory disease mechanisms (e.g. elevated levels of systemic cytokines) (Bartold et al., 2005). In particular, the osteoclast pathway is galvanized by an

alteration in immune status, accompanied by chronic inflammation; the latter is a typical condition in periarticular osteoporosis and local bone destruction around the joints (Ono et al., 2013). It has been reported that, in an observed population, 94.6 % of the patients were given a therapy of DMARDs; 82.5 % of the patients receiving methotrexate additionally received folic acid; and 65.9 % of the patients received calcium and vitamin D(Hartmann et al., 2008) and glucocorticoids. In order to prevent or treat primary or secondary osteoporosis, RA patients take bisphosphonates (BPs): prescription of nitrogen-containing bisphosphonate (NBP) or non nitrogen-containing bisphosphonate (NBP) are frequently used. Alendronate has been the most prescribed oral NBP formulation (Piscitelli et al., 2014) and, to date, it has been frequently related to the severe BP-related adverse drug reaction named as osteonecrosis of the jaw BRONJ (bisphosphonate-related ONJ) (Di Fede et al., 2013). Firstly, BRONJ was observed by Marx and Stern in 2002. Extensive case series regarding BRONJ were published in 2003 by Marx and in 2004 by Ruggiero *et al* (Marx, 2003, Ruggiero et al., 2006); currently, an increasing number of publications relating to BRONJ is available in the literature. Recently, BRONJ was defined by Bedogni *et al*. as a "progressive destruction and death of bone that affects the mandible and/or maxilla of patients, exposed to treatment particularly with NBPs, in the absence of a previous radiation treatment (Bedogni et al., 2012)". In subjects exposed to NBPs, following a localized trauma, such as tooth extraction, the jaw could generally fail to heal, leaving the bone exposed in many cases (Capsoni et al., 2006). There are, however, numerous reports describing ONJ with symptoms and/or minor signs but in the absence of bone exposure (Fedele et al., 2010, Mawardi et al., 2009, Bedogni et al., 2014). Bone lesions can be observed more frequently in the mandible and less in the maxilla(Vescovi et al., 2012, Otto et al., 2012, Khan et al., 2015); both mandible and maxilla have been found in different percentages (5-11.1%)(Otto et al., 2012, Gammelager et al., 2013). Furthermore, other antiangiogenics (e.g. bevacizumab) and/or antiresoptive (e.g. denosumab, sunitinib) drugs have been associated with ONJ (Cardona Tortajada et al., 2014, Fedele et al., 2015, Fangusaro et al., 2013, Fusco et al., 2014).

The epidemiology of ONJ remains unclear due to the inconsistency and limitations of available studies. These include: a lack of a specific ICD code; under-reporting in Surveillance Drug Systems; a recent introduction of preventive measures; case adjudication restricted to exposed ONJ; short-term observation; and a lack of cumulative long-term incidence rates(Campisi et al., 2014). Very recently, English authors have estimated that the incidence of ONJ in the oncological and osteometabolic population is approximately 10 cases/million/year(Rogers et al., 2014). A wide-ranging incidence of ONJ from 0% to 27.5% has been reported for individuals exposed to intravenous BP(Kuhl et al., 2012). In patients receiving oral NBPs, ONJ data should be treated with caution. (Reid, 2009). Generally, a prevalence of ONJ ranging from 0.001% to 0.4% (Conte-Neto et al., 2012, Malden & Lopes, 2012, Lo et al., 2010, Landesberg & Taxel, 2013) has been reported in RA patients. Whilst the pathogenesis of ONJ is unclear, various risk factors are not well recognized and they are usually categorized into three groups: drug-related, local, and demographic/systemic risk factors (2007, Ruggiero et al., 2006). Of the systemic risk factors, Rheumatoid Arthritis (RA) has been markedly considered (Park et al., 2010, Malden et al., 2009), although a comprehensive study has yet to be performed.

Rationale

The case reports of a few RA patients (Conte Neto et al., 2011, Conte-Neto et al., 2012, Conte-Neto et al., 2011, Manzon et al., 2014, Alsalleeh et al., 2014, Ebker et al., 2013, Junquera et al., 2009, O'Ryan & Lo, 2012, A. Fasciolo, 2014, A. Nori, 2014) have been described in the literature. In addition to discussing the prescription of NBPs for treating or preventing cases of osteopenia/osteoporosis, further factors leading to ONJ in RA patients have been hypothesized: chronic inflammatory alterations (Conte Neto et al., 2011); the immuno-suppressive action of corticosteroids (Coutinho & Chapman, 2011); and MTX (Herman et al., 2004) predisposing to local infections

(Fleischmann et al., 2006). In order to reduce any bias and to verify a possible link between RA and ONJ, multicentric studies are required.

METHODS

Study design

A retrospective cohort study was reported according to the STROBE (*Strengthening the Reporting of Observational Studies in Epidemiology*) recommendations(von Elm et al., 2014). The Ethical Committees of the participating centres approved the study (N 4/2012 18-04-2012) and patient consent was obtained where specifically required.

Setting

Researchers at the Universities of Palermo, Verona and Padua designed the study and sent a collaboration proposal to their centres of Oral Medicine and/or Maxillofacial Surgery with a special interest in the diagnosis of ONJ in patients affected by RA.

Participants

Selection and eligibility criteria

Patients, referred to the participating centres between January 2004 and December 2011, were eligible for our study if: 1) they were affected by RA; 2) had previously had, or were currently having, treatment with bisphosphonates and/or denosumab; 3) they had exposed ONJ (defined as the presence of long-standing - > 8 weeks - transmucosal exposure of necrotic jawbone (Ruggiero et al., 2009)) or non-exposed ONJ (defined as the presence of otherwise unexplained jawbone pain, fistula, swelling, mobile teeth or mandibular fracture, as defined by Fedele *et al* (Fedele et al., 2010)); 4) they had no history of head-neck radiotherapy; and 5) there existed CT scan imaging (spiral or cone-beam) of the affected jawbones. Only patients with CT scans performed within 6 months from clinical phenotyping were included, in order to have a concordance between clinical manifestations and CT findings. Dentascan reformatted images were not considered as they do not accurately display the ramus of the mandible and the midfacial bones.

Criteria for exclusion were off-label use of BPs and the presence of associated tumor growth in the jaws. ONJ case-adjudication throughout all the centres was performed by multidisciplinary teams which included BP prescribers and specialists in Oral Medicine and/or in Maxillofacial Surgery. Each report was supported by a qualitative case-by- case assessment procedure, which was performed by an officially – recognized drug expert.

Data collection and variables

The hospital notes of consecutively diagnosed ONJ patients were retrospectively reviewed between June 2012 and September 2013. The following data (clinical, radiological measurement) relevant to the study were extracted by local clinical teams and entered into a pre-defined electronic case report form by one clinician at each institution.

The following *clinical measurements* were collected from the clinical charts: 1) age; 2) sex; 3) underlying bone disorders and co-morbidities; 4) NBP type; 5) duration of NBP treatment; 6) NBP cumulative dose; 7) the simultaneous or select use of antiresorptives (e.g. denosumab); 8) the concurrent use of steroids and/or methotrexate; or 9) other drugs, such as antiangiogenic agents (i.e. sunitinib and bevacizumab); 10) the time period leading up to ONJ onset; 11) the presence of known risk factors for ONJ (tooth extraction, dental or periodontal infection, an ill-fitting prosthesis and dental implant surgery); 12) the ONJ site; 13) the presence of exposed bone; and 14) the presence of minor clinical signs and symptoms.

Radiologic measurements were analyzed by panoramic radiograph and computed tomography (CT)

The staging of the disease was based on the current clinico-radiological staging system, as proposed by SICMF-SIPMO(Bedogni A, 2013).

Statistical analysis

The two responses of the study were *bone exposure*, coded as *negative* or *positive*, and the *ONJ stage*, coded according to SICMF-SIPMO and dichotomized as stage 2 or 3 vs stage 1. [49]. To summarize demographical data and outcomes, categorical values were expressed as counts and percentages %. Quantitative variables, such as NBP cumulative dose (mg) and NBP duration (months), were expressed as the median value and the interquartile range (the 25th and 75th percentiles). At univariate analysis, the association of both responses with pharmacological, systemic and clinical variables, and the association between either corticosteroid therapy or tooth extraction with NBP features were tested using the Fisher's exact test. Furthermore, crude Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated as association measures. NBP duration and cumulative dose were dichotomized using the median value. Aledronate was chosen as a reference for the type of administered NBP. Multivariate analysis was not performed, in the absence of statistically significant variables at univariate analysis. A p value < 0.05 was chosen to represent statistical significance. Data were analysed using STATA SE, v. 14.1.

RESULTS

Details of the study population: Eighteen patients affected by RA and ONJ were considered eligible: 16 patients were females and 2 males, the median age was 69 years (interquartile range 63-72 years). Sixteen (88.9%) patients were in therapy for RA: 9/18 (50.0%) with systemic steroids, 3/18 (16.7%) with methotrexate, and 4/16 (22.2%) with steroid and methotrexate. Two RA patients declared that they were not currently receiving any treatment. All patients suffered from secondary osteoporosis and 11/18 (61.1%) showed further morbidities (e.g. diabetes, coagulopathy). All had been treated with bisphosphonates. More than half (11, equal to 61.0%) of the patients were treated with aledronate, and three of them also received another NBP. Four patients (22.2%) were treated with Ibadronate, 2 (11.1%) with Risedronate and 1(5.6%) with Zoledronate. In the subgroup of patients who had only used Alendronate, the median cumulative dose was 15120 and the median duration of NBP therapy was 69 months. The mandible was affected by ONJ more frequently (66.7%) than the maxilla (33.3%), and one patient presented more than one localization of ONJ (mandible and maxilla). ONJ appeared as exposed in 11 (61.1%) patients and as the non-exposed variant in 7 (38.9%) subjects. Regarding the ONJ staging, according to Bedogni (Bedogni et al., 2012): 4 patients had stage 1 ONJ (22.2%), 11 patients had stage 2 (61.1%) and 3 patients had stage 3 (16.7%). Tooth extraction (due to dental/periodontal diseases) was identified in 9 (50.0%) patients as a trigger ONJ event. There was evidence of periodontal chronic disease in 5 (27.8%) subjects, prosthetic trauma in 1 (5.6%) case and dental implant infection in 3 other cases (16.7%). Of note, implant surgery was carried out before NBP administration in all cases. Other clinical and pharmacological records of the sample are shown in Table 2.

When bone exposure was associated with pharmacological, systemic, local and clinical variables, no significant association was found (Table 2). Neither treatment with corticosteroid therapy nor tooth extraction as an ONJ trigger event were significantly associated with NBP features (Table 3).

DISCUSSION

Osteonecrosis of the jaw (ONJ) is a rare and serious adverse side event, particularly related to the administration of NBPs. Its epidemiology and pathogenesis remain for the most part unclear although significant improvements have been made regarding its definition, diagnosis and staging, prevention strategies and treatment; additional risk factors have yet to be recognized.

Generally, the effective risk of ONJ in patients treated with NBPs for osteometabolic diseases is not particularly well-known, in part due to the paucity of crucial information. The latter include the exact total number of patients exposed to NBPs and the precise interplay of the elevated number of potential risk factors implicated. Even less is known about ONJ risk in RA patients. NBPs are the main drugs associated with ONJ but they are not the only ones. Indeed, denosumab, which has recently been used to treat secondary osteoporosis, is also considered to be ONJ-related. Systemic steroids and methotrexate MTX are generally prescribed, also in combination, to manage chronic diseases such as RA, a systemic autoimmune disease characterized by progressive joint destruction and a variety of systemic manifestations resulting from chronic inflammation. Although RA has been proposed as one of the risk factors of ONJ (Conte-Neto et al., 2011), no RCT has been published for establishing the effective association between ONJ and RA, and fewer papers discussing epidemiological data have been produced.

Several relevant factors linking RA and ONJ have been discussed(Conte Neto et al., 2011): the role of steroids and other immunosuppressive agents, such as MTX for the inhibition of bone remodeling; NBP could increase the arthritic process, thereby increasing flogosis; the antiangiogenic activity of NBP determining the loss of blood vessels; inflammation by RA due to its deleterious effects on bone tissues directly or by mediators; concomitant diseases, such as periodontitis and osteomyelitis, which are common in RA patients; and NBP and/or MTX toxicity theory. NBPs exclusively affect the phagocytic cells and not other types of cells and the local immune response could also be compromised. Indeed, since bisphosphonates do not affect neutrophils, the risk of systemic infection is low. The reduced function of monocytes and macrophages could become critical for the development of ONJ (Pazianas, 2011).

Some of aforementioned and controversial hypothesis have been recognized in our study: the majority of the ONJ patients (88.9%) were undergoing therapy with steroids and/or MTX to treat RA, and many local inflammatory features were recognized; on the other hand, in 5/18 (27%) who did not take GCs, other factors (such as MTX therapy or flogosis activation) could play a predominant role. Moreover, there were other two subjects who had never been in treatment for RA either with systemic corticosteroids or MTX and they presented even more advanced conditions of local flogosis than the RA patients undergoing therapy. The authors of these points consider them to be very important in taking them into account regarding an ONJ prognosis. Indeed O'Ryan and Lo (O'Ryan & Lo, 2012) have recently observed that ONJ patients taking oral BPs with relevant comorbidities, such as RA, had a lower probability of healing and a longer median time in healing than patients without comorbidities.

Some years ago, an extended literature review (Conte-Neto et al., 2012) was conducted with the aim of evaluating important issues relating to RA patients who had developed ONJ, including demographic, clinical, and treatment aspects. The goal of this study was to establish comparative associations between patients without RA but who had developed oral BRONJ. Different research was compared with different descriptive procedures and considered variables. The sample of data discussed in this Paper was collected in accordance with the same research protocol, applying and aggregating data from different regions (a multicenter study). This, therefore, reduced the probability of missing data, thereby producing a homogeneous sample. RA patients who developed ONJ lesions after an oral NBP intake were usually female, 60+ years old, as has already been observed by other researchers (Conte-Neto et al., 2011). In the patient group in this study, alendronate – an oral NBP – was found to be that most associated (61.1%) with osteonecrosis. It is also the most prescribed drug for preventing and treating osteoporosis, as confirmed by Malden and

Lopes (Malden & Lopes, 2012). The duration of NBP in the RA patients with ONJ in this study varied from 1-130 months, similar to that previously reported (2-120 months) (Di Fede et al., 2013) in the osteoporotic case series. Moreover, it is notable that the longer-term use of oral NBPs, as is usual for RA therapy, may have a dose equivalence effect, potentially approximating to that of BP levels in bone, which is thought to be achieved only through high-dose intravenous delivery.

Of note, it is interesting to observe the absence of spontaneous ONJ in our sample, that is, when any systemic and/or local risk factors were not recognized: excluding the presence of RA, whose hypothesis of ONJ onset was not defined, one or more ONJ risk factors were recognized in every patient. Thus, the presence of RA might lead to enhanced susceptibility, as previously speculated, even if evidence for this is currently lacking.

In order to evaluate the site and characteristics of ONJ in the RA patients in this study, we observed that the mandible was most prevalently involved (61.1%) and this fact has been published by other researchers in the field (Diniz-Freitas et al., 2012, Di Fede et al., 2013). Furthermore, a high percentage of cases (38.9%) did not present bone exposure but they did display minor clinical and radiological signs, according to Bedogni *et al* (Bedogni et al., 2012).

In conclusion and in light of the data presented in this Paper, it could be hypothesized that patients with RA, when exposed to NBP, may be more susceptible to ONJ than the majority of osteometabolic patients. Evidently, one significant limitation of our research is the absence of RCTs dealing with this issue. This surely points to the direction of future research.

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Table 1- Demographical data and outcomes.

AR + BRONJ analyzed patients	**18**	
Median age (yrs)	69	
Interquartile range (yrs)	63-72	
Mean age±SD (yrs)	68.0±8.	
	n(%)	
Gender		
Female	16 (88.9)	
Male	2 (11.1)	
	YES	**NO**
Other comorbidities	11 (6.1)	7 (38.9)
AR therapy		
Corticosteroid therapy	13 (72.2)	5 (27.8)
Methotrexate therapy	7 (38.9)	11 (61.1)
Other drugs		
Denosumab therapy	1 (5.6)	17 (94.4)
Type of administered NBP	**n(%)**	
Alendronate§	11 (61.)	
Ibadronate	4(22.2)	
Risedronate	2(11.1)	
Zoledronate	1(5.6)	
Mono NBP	15 (83.3)	
Poli NBPs	3(16.7)	
	Range	**Median (Q_1-Q_3)**
NBP duration (months)	20-130	69 (48-99)
NBP cumulative dose (mg)	5-36400	15120 (0-27720)
BRONJ site		
Mandible	12(66.7)	
Maxilla	6(33.3)	
		42.1
	YES	
Bone exposure	11 (61.1)	7 (38.9)
BRONJ staging (ref SICMF-SIPMO)		
Stage 1	4 (22.2)	
Stage 2	11 (61.1)	
Stage 3	3 (16.7)	
Trigger event (Local risk factors for BRONJ)	**YES**	**NO**
	18(100.0)	0(0.0)
Tooth extraction	9 (50.0)	
Periodontal infection	5 (27.8)	
Prosthetic trauma	1 (5.6)	
Implant infection	3 (16.7)	

§ 3 of 12 patients treated with Alendronate receive also another NBP

Table 2 - Statistical significance of the univariate association between bone exposure and SICMF SIPMO staging with pharmacological, systemic and clinical variables.

	Bone exposure	SICMF SIPMO staging
Type of administered NBP	0.589	0.112
NBP cumulative dose[2]	1.000	0.576
NBP duration[3]	1.000	1.000
Implant infection	1.000	1.000
Periodontal infection	0.596	0.278
Prosthetic trauma	0.3891	1.000
Tooth extraction	1.000	0.082
Other comorbidities	1.000	1.000
Corticosteroid therapy	0.326	1.000
Methotrexate therapy	0.637	1.000
Denosumab therapy	1.000	1.000
BRONJ site	0.627	1.000

[1]Fisher's exact test p-value. p-values<0.05 were statistical significant
[2]Cumulative dose >15120 vs <=15120 (Median value); [3]Duration>69 vs <=69 (Median value)

Table 3

	Steroids	Tooth extraction
Type of administered NBP	1.000	0.506
NBP cumulative dose[2]	1.000	1.000
NBP duration[3]	1.000	1.000