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Title: OSTEONECROSIS OF JAW (ONJ): IMPACT OF ITALIAN PATIENTS, AND
ROLE OF ITALIAN PHYSICIANS, DENTISTS, AND RESEARCHERS IN THE
GROWING EVIDENCE OF A "NEW" DISEASE

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Abstract

Purpose: Osteonecrosis of jaw (ONJ) is an uncommon but severe complication observed mostly in patients treated with bisphosphonates (BPs) for bone metastases, myeloma, osteoporosis (so called BRONJ, Bisphosphonate-Related Osteonecrosis of Jaw), but also with other drugs (bevacizumab, sunitinib, denosumab). The number of cases observed in Italy appears high in comparison with other countries and we present a review of several aspects of ONJ in Italy and the role of Italian health professionals and researchers on increasing knowledge and adequate reporting of ONJ phenomenon;

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Methods: Literature review about osteonecrosis of jaw (ONJ) with selection of Italian authors and publications, on year 2003-2011, by research on international electronic journal databases, Italian language journals, congress acta, web sources;

Results: at October 2011, among 1272 papers published worldwide on ONJ issue, 128 (10%) were from Italian Authors;

Conclusions: relevant articles by Italian groups were published about pathogenesis hypotheses, animal models, biology studies, risk factors, preventive measures, dental extraction protocols in BP-exposed patients, laser therapy, ozone therapy, surgical treatment. Experience of Italian patients suffering from ONJ, together with work of Italian dentists, physicians and researchers, appears of paramount importance in order to study ONJ and minimize a possible severe side-effect of efficacious medical treatments.

1. Introduction

Osteonecrosis of jaws (ONJ) has been largely described since first 2000 years [1-4] in patients receiving bisphosphonates (BPs), drugs widely administered for the treatment of bone disease in multiple myeloma and metastatic solid tumors but also in osteoporosis and other non-malignant bone pathologies. The mechanisms underlying the development of Bisphosphonate-Related ONJ (BRONJ) are not completely understood [5-6]. Furtherly, ONJ has been recently observed also in patients treated with other drugs, such as bevacizumab, sunitinib, and denosumab [7-9]. In Italy, the number of BRONJ cases observed is particularly high in comparison with other countries [10]. We present a review of several aspects of ONJ in Italy and the role of Italian health professionals and researchers on increasing knowledge and adequate reporting of ONJ phenomenon.

2. Material and methods

A manual searching was performed using a full text electronic journal database (Pub Med); the main applied key was "Osteonecrosis AND (jaw OR jaws)", and publications including Italian authors were selected.



Further research was conducted on Pub Med using terms : "Diphosphonates" [Mesh] OR Bisphosphonate* OR Diphosphonates*", "Breast Neoplasms" [Mesh], "Prostatic Neoplasms" [Mesh], " Multiple myeloma " [Mesh] AND "osteonecrosis".

Italian language journals (of oncology, haematology, maxillofacial surgery and dentist interest) not included on Pub Med were reviewed, since 2003 to October 2011.

National and international congress and conference acta (abstract books, educational books, highlights, etc.), both in English and Italian language, were examined to search possible contributions of interest.

Reports from AIFA (the Italian Drug Surveillance Agency) including ONJ cases and recommendations were considered. Guidelines from several Italian scientific societies and deliberations from Italian Ministry of Health about prevention and early diagnosis of ONJ were examined.

Further papers, recommendations, position papers, books, documents were found by a manual searching on the web.

3. Results

Pub Med publications

Between 2003 and October 2011, a large amount of articles have been published worldwide on ONJ issue (1272); 10 % of them (128) were from Italian Authors. We classified the latter items as follows: 38% are case reports and clinical experiences; 13 % report a therapeutic or behaviour protocol; 32% were about therapy; 13% were guidelines about preventive measures; 15% were literature reviews.

The analysis showed that 55% of publications by Italian authors were issued in the last three years (2009-2011), representing the increased interest and recent work of Italian physicians and researchers towards ONJ.

BRONJ pathogenesis hypotheses, animal models, pathological and genetics studies were objects of papers by several groups, located in Verona [11-12], Trieste [13] , Torino [14-15] , Florence [16], Bari [17] , Messina [18-21], and other academic centers [22-24].

Several BRONJ case reports and case series in cancer and myeloma patients have been published since first years of BRONJ appearance [25-40]. Particular case reports included one case of BRONJ associated to osteonecrosis of left thumb [41], BRONJ diagnosis years



after BP discontinuation [42], BRONJ in a hemodialysis patient [43], ONJ in a leukaemia patient not treated with BPs [44], BRONJ associated with photodynamic therapy [45].

BRONJ incidence (or prevalence, or frequency) data have been evaluated and discussed by Italian authors : in breast cancer patients [27,33,46-47], in prostate cancer patients [48-49] , in myeloma patients [50-54] , and in mixed neoplasms patient series [54-57] .

Large (more than 100 BRONJ cases) single-centre experiences have been published, such as that of Parma [58] and Catania [59] , or are under reviewing (e.g. Verona, Palermo, Rome, Milan, etc).

One regional experience (247 cases in Piemonte-Valle d'Aosta area, on years 2005-2008) has been published only as a summary, at this date [56, 60] .

A multicenter case collection of 672 BRONJ cases observed in several Italian centers, collected on 2009, is under evaluation and has generated one published article [61] and other papers under authors' discussion or under submission.

ONJ definition and staging were examined by several Italian researchers, who underlined problems concerning cases without bone exposure and the so-called "stage 0 " according to the AAOMS staging system [62-63] ; a proposal for a new staging system is under discussion by members of a panel prompted by Italian societies of maxillofacial surgeons (SICMF) and oral care specialists (SIPMO).

Imaging studies have been performed [64-69] and others are submitted or ongoing.

Risk factors are fundamental to know odd ratio of single patients. Systemic risk factors, such as type of BP (with zoledronic acid linked to higher risk) [46, 53] and treatment duration and schedule [53,70-72] have been studied; after-treatment residual risk was reported [42]. Local (dental) risk factors, including tooth extractions [70] , periodontal disease [25] , and dental implant [73-75] have been underlined.

About preventive measures, Italian authors published proposals of risk management [76-84] but also efficacy studies [85-86] and general population evaluations [60].

Dental extraction protocols in BP-exposed patients have been reported by several groups [12, 75, 87-89] in order to minimize the risk of ONJ after dentoalveolar trauma.

BRONJ in non-malignant diseases, mostly osteoporosis patients, was critically evaluated [80,82, 90-91] , with increased reports in latest years [73, 92-94]; Italian authors were included in an international multi-centre study [95] .



Reports and evaluations by Italian authors about ONJ in patients receiving other drugs (with or without BPs) have been published; they included bevacizumab [47, 96], sunitinib [97-98], denosumab [10] .

Uncertainty of efficient BRONJ treatment options was examined by several Italian groups [39, 55, 61, 99- 101]. Conservative treatments were indicated as fundamental by some authors [59, 93, 102-103] . Surgical treatment series or case reports have been object of several papers [61,104-111] , including a prospective experience of large jaw resections with long-term follow-up [112] .

The first case of autologous bone marrow stem cell intralesional transplantation to repair BRONJ has been recently published by an Italian centre [113] .

Laser therapy, with different instruments, was proposed by several groups [114-119] .

Also ozone therapy has been applied in different forms [120-123] , and comparison studies are needed to confirm its usefulness.

Italian language publications

In years 2004-2011, at least 84 Italian language articles (reviews, case reports, case series) and abstracts have been published (mostly in dentist Italian literature, but often on websites or web journals), even from physicians and centres not publishing on Pub Med journals .

Two Italian language books [124-125] and the translation of a textbook by RE Marx [126] have been printed.

AIFA reports

Since 2005, numerous reports from AIFA (the Italian Drug Surveillance Agency) included ONJ case series and prevention recommendations. However only a little part of ONJ cases published in literature and/or reported at congresses and conferences are also signalled to the Agency, due to a poor attitude of Italian physicians and dentists to centralized drug side-effect reporting (only 425 BRONJ cases had been reported to the national Drug Surveillance System as of June 2009) [127].

The AIFA offices actively worked with European Agency (EMEA, now EMA) on discussing ONJ phenomenon [128], both related to BP treatment and to other drugs (antiangiogenic agents) [129], collaborating on releasing of bevacizumab and sunitinib alerts on autumn 2010 [130, 131, 132] .



Italian Congresses

Beside capillary local/regional dentist conferences (mostly organized by ANDI, the Italian National Dentist Association) and local medical oncology/haematology symposia, we found ONJ-dedicated sessions or presentations in national congresses of several societies. Italian societies of maxillofacial surgeons (SICMF), oral pathologists and care specialists (SIPMO), oncologists (AIOM), haematologists (SIE) organized oral presentations, issue symposia and abstract discussion sessions in their congresses in latest years. Furtherly, dozens of abstracts and posters about BRONJ have been offered by scholars and students at annual meetings of the Italian college of oral care teachers ("Collegio dei Docenti di Odontoiatria").

Moreover, some specific-issue national conferences (Alessandria 2007, Messina 2008, Alessandria 2008-2009-2010) were organized, with dozens of abstracts and reports from centers of all the Italian regions (only minimally later published as full papers). Highlights of those national congresses have been diffused by Italian language newsletters [133] and most of contributions are available on a website (www.reteoncologica.it.) [134].

European and International Congresses

Abstracts from Italian Authors about ONJ appeared in the acta of many international society congresses, such as ASH (American Society of Haematology), ASCO (American Society of Clinical Oncology), EHA (European Haematology Association), ESMO (European Society of Medical Oncology), ECCO (European Cancer Organization), EAOM (European Oral Medicine Association), EACMFS (European Association of Maxillo-Facial Surgeons), and international conferences (for example SABCS, San Antonio annual breast cancer symposium).

Recommendations, guidelines, position papers

Beside an official recommendation by Italian Health Minister [135], documents about ONJ were approved and diffused (or are going to be published) by several Italian societies and study groups: SICMF-SIPMO panel (an expert panel organized by Italian societies of maxillofacial surgeons and oral medicine specialists), AIOM (oncologists), SIF (pharmacologists), SIOMMMS (bone disease specialists), GISBI (BP study group), PROOF (dental legal experts), Rete Oncologica Piemonte-VdA (multidisciplinary study group about BP prescription in cancer and myeloma), etc.



Epidemiologic data

Systematic BRONJ case collection has been pursued on two regional area.

In Piemonte – Valle d’Aosta (4.3 million population), inside a regional oncology network (Rete Oncologica Piemonte Valle d’Aosta), on November 2005 a BRONJ multidisciplinary study group was created, after observation of 60 cases in few referral centers [136]; enlargement of the group to 37 oncology / haematology regional units and 19 oral care units pushed a systemic collection up to 247 cases on December 2008 [60] .

In Sicily, a local drug side-effect surveillance system (hospital pharmacist network) has collected 102 cases in 3 referral centers of two cities (Palermo and Messina) on years 2008-2009 [137] and is enlarging to all the region.

4. Discussion

In recent years many Italian groups have published a large amount of articles about several aspects of ONJ in English language peer-reviewed journals, reporting an high number of observed patients. An even larger amount of ONJ cases (mostly BRONJ in cancer and myeloma patients, but with increasing number in not malignant diseases) has been illustrated in national and international congresses and conferences. We calculated that Italian authors have reported between 2005 and 2009, either in congresses, dedicated annual meetings [133-134] and/or peer-reviewed journals, at least 1,200 different ONJ cases (among which are 672 cases from a multicenter survey, whose results are only partially published) [61]. Everyone could imagine that many other cases have not been reported at all.

Projecting to whole Italian population (58 million) the number of BRONJ cases (247) observed in Piemonte-Valle d’Aosta (4.3 million) in years 2004-2008 [60] , one could speculate that more than 3000 BRONJ cases have occurred in Italy in those years.

Why so many BRONJ cases in Italy, especially among cancer and myeloma patients? Looking for the main reasons, we invite readers to consider several possible facts. Firstly, on the basis of prescriptions in years 2002-2008 of zoledronic acid (the mostly administered iv BP, largely replacing pamidronate) (fig 1), we can consider that iv BP consumption rate in metastatic bone and myeloma patients in recent years was higher in Italy than in other European countries (with exception of Belgium) (AIFA personal communication) (fig 2); drug therapy is largely covered by the national public Italian Health System (SSN, Sistema Sanitario Nazionale), and this is totally free for oncology and haematology patients , in years



2001-2006 largely treated with BPs in public and private centres, on a monthly basis, accordingly to less recent guidelines indicating continuous BP treatment “*until evidence of substantial decline in a patient's general performance status*” [138-140] . Secondly, on the contrary, the SSN did not adopt adequate coverage for oral health measures, that are mainly left to individual choice and are *mostly* under care of private dentists; direct and indirect measures indicate an insufficient median status of oral health in Italian people, especially of middle-age and elderly people (the age in which you can find most of cancer and myeloma patients). Consequently, the sum of systemic factors (large amounts of iv monthly BPs, for prolonged time, particularly of zoledronic acid) and of local factors (bad oral health status; periodontal disease; high number of teeth needed to be extracted without specific protocol during BP treatment; etc) could explain such a high number of BRONJ cases in years 2004-2008.

In Italy diffusion of knowledge of BRONJ among specialists and medical and dentist practitioners was late in comparison with North America. In USA, since 2004 Novartis Pharmaceuticals Inc , the major manufacturer of large-diffused iv bisphosphonates, pamidronate (Aredia®) and zoledronic acid (Zometa®) alerted involved specialists (oncologists, haematologists, dentists, maxillofacial surgeons) with a “white paper” drawn up in March 2004 and made public in June 2004, followed by a “dear doctor” letter (September 2004); patients were even alerted through meetings with patient advocacy groups since May 2004 and the diffusion of a patient information booklet [4]. In Italy , only on late 2005 and on 2006, after stimulation [141] and after first publications on main international medicine journals [142], BP manufacturers and health authorities adopted measures to inform involved specialists. Afterwards, especially since 2007, information about this “new disease” was diffused, also among dentist practitioners. However, also in Italy [143] as well as in other countries [144-145] patients ignorance about administered BP treatment , as well as dentists and physicians insufficient information, remains a substantial risk factor for inducing new cases of BRONJ .

On the other side, the reduction of number of new BRONJ cases in latest years in some large Italian referral centers (data not yet published) as well in one regional area [60] seem indicate encouraging results from adoption of preventive measures, together with a more selective use of BPs (as indicated by more recent guidelines) [146-147] .

In conclusion: experience of Italian patients suffering from ONJ, together with work of Italian dentists, physicians and researchers, appears of paramount importance in order to



study ONJ and minimize as much as possible this severe side-effect of efficacious medical treatments.

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FIGURES

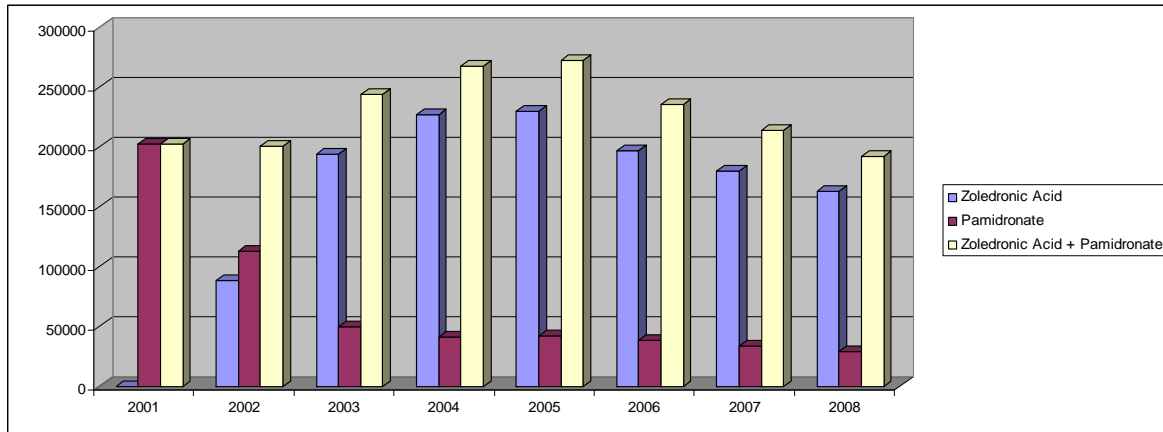


Figure 1: Number of prescribed units of pamidronate (1 unit = 90 mg) and zoledronic acid (1 unit = 4 mg) in Italy between 2001 and 2008 (elaboration from AIFA data, personal communication).

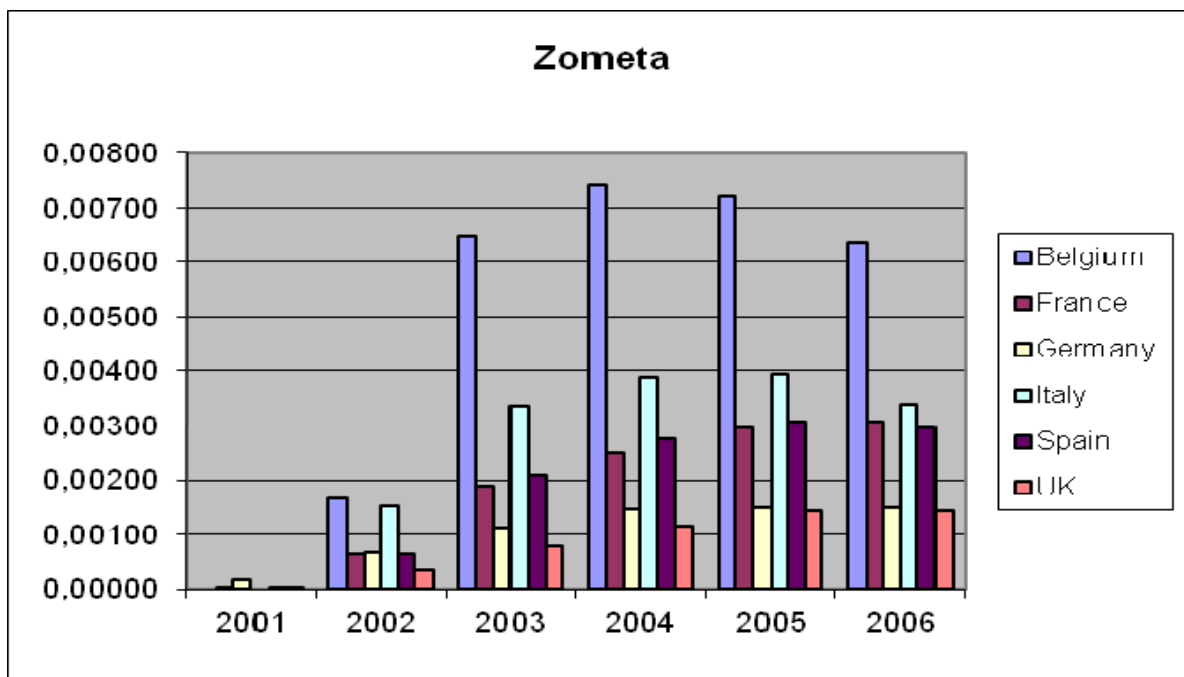


Figure 2: Rate of prescribed units of zoledronic acid (1 unit = 4 mg) in Italy between 2001 and 2006, per million of inhabitants, in several European countries (elaboration from AIFA data, personal communication).