Bisphosphonate-related osteonecrosis of the jaws – A review

Sebastian Kühl, Christian Walter, Stephan Acham, Roland Pfeffer, J. Thomas Lambrecht

Aims: The aim was to evaluate the knowledge about bisphosphonate-related osteonecrosis of the jaws (BRONJ). A bibliographic search in Medline, PubMed and the Cochrane Register of controlled clinical trials was performed between 2003 and 2010 by using the terms bisphosphonate and osteonecrosis of the jaw. The amount of publications per year, the type of journal for publication, and the evidence level of the trial were evaluated. Next to this the incidences and the success of treatment strategies for BRONJ were identified. A total of 671 publications were reviewed, mostly in dental journals. The evidence level could be determined for 176 publications and only one grade Ia study was found. The studies showed a wide variety in design, most of them being retrospective. The incidence of BRONJ is strongly dependent on oral or intravenous application and varies between 0.0% and 27.5%. There is no scientific data to sufficiently support any specific treatment protocol for the management of BRONJ. Further clinical studies are needed to evaluate the incidence and treatment strategies at a higher level of evidence. Therefore uniform study protocols would be favourable.

Keywords: Diphosphonates; Osteonecrosis of the jaw; Incidence; Treatment outcomes

Introduction

Bisphosphonates are frequently used for the treatment of bone metastases, multiple myeloma, osteoporosis and other bony diseases. Generally these drugs are well tolerated, rarely inducing clinically significant side effects such as gastrointestinal symptoms for oral bisphosphonates, elevated serum creatinine, transient low-grade fever, arthralgias and increased bone pain for the injectable drugs. However, recent reports have described osteonecrosis of the jaw bones (ONJ) as a potentially serious complication related to the long-term use of these drugs. In this condition the bone tissue in the jaws often fails to heal after minor trauma, such as tooth extraction, leaving the bone exposed. Bisphosphonate-related osteonecrosis of the jaws (BRONJ) was first described by Marx and Stern in 2002. The first extensive case series of BRONJ were published in 2003 by Marx and in 2004 by Ruggiero et al. Since 2003 there has been an increasing number of publications about BRONJ. One of the first retrospective studies by Estilo et al. was published in 2004. Cases of BRONJ were published in refereed journals, abstract presentations at scientific meetings, correspondence in the form of letters to the editor, author’s replies and editorials as well as medical alerts and advisories to dentists and physicians. The similarity of BRONJ to cases of phosphorous osteonecrosis of the jaw in workers exposed to white phosphorus (phossy jaw) during the late 19th and early 20th century has been reported by Hellstein et al. and Donaghue. This historical fact led to the suspicion that the phenomenon of jaw osteonecrosis was directly linked to the bisphosphonate medications.

Many groups and societies have recently published recommendations or guidelines on the prevention, staging and management strategies for BRONJ. Despite these recommendations there is still a lack of information concerning the incidence, pathogenesis, treatment strategies and prevention of BRONJ. Until now a classification of all publications according to the evidence level of Shekelle et al. has not been published. There is no knowledge about the number of publications per year as well as the type of journals for publication. The aim of the present study was to perform a literature search in order to (a) assess the number of publications per year; (b) evaluate the type of journals for publication; (c) determine the level of evidence of published trials for classification; (d) retrieve information on the incidence; and (e) the treatment strategies and results related to BRONJ.

Materials and methods

Search strategy

A bibliographical search in Medline, PubMed and the Cochrane Register of controlled clinical trials was performed for publications...
which appeared in the period from January 2003 up to March 2010 using the terms: Bisphosphonate and osteonecrosis of the jaw. The cited literature was evaluated and a traditional manual search and library research was additionally performed.

**Study selection**

In a first evaluation, papers were selected according to whether or not they deal with BRONJ. All manuscripts, including case reports, were selected for evaluation of the number of publications per year. The journals in which these publications appeared were assigned to a specific medical field according to Table 1. In a second step, all clinical studies were extracted and the grade of evidence was classified for every clinical study according to the classification of Shekelle et al.29 as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category of evidence</th>
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<tbody>
<tr>
<td>Ia</td>
<td>Evidence from systematic reviews of randomized controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence from at least one randomized controlled trial</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence from at least one controlled study without randomization</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence from at least one other type of quasi-experimental study, such as time series analysis or studies in which the unit of analysis is not the individual</td>
</tr>
<tr>
<td>III</td>
<td>Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, cohort studies and case-control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from expert committee reports or clinical experience of respected authorities</td>
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</table>

For the evaluation of the incidence and the success of therapeutic strategies of BRONJ, publications had to reach the level of evidence of at least grade IV. Studies which did not reach the lowest grade IV, representing evidence based on expert committee reports or clinical experience of respected authorities, were excluded from evaluation of the incidence and therapeutic outcomes.

Therapeutic outcomes were categorised into two groups: conservative treatment and surgical treatment. Conservative treatment was defined as pain control and local disinfection by mouth rinse and, if applied additionally, antibiotic therapy. Limited débridement in terms of removing unfixed necrotic bone without surgical exploration was also defined as conservative treatment. Surgical treatment was defined as any invasive act in which rotating instruments or others were used for osteotomy and resective surgery of necrotic bone.

**Data extraction**

Data were extracted based on prefabricated spreadsheets using Microsoft Excel (Microsoft Office Excel 2007, Redmond, USA). Any obscurities were evaluated by at least two reviewers independently. A third reviewer compared the evaluation and data were discussed. Data were only included if there was an agreement between the reviewers.

**Statistical analysis**

All data were saved in spreadsheets. The statistics are restricted to a descriptive analysis only. The absolute numbers and percentage distribution were calculated using Microsoft Excel (Microsoft Office Excel 2007, Redmond, USA).

**Results**

**Numerical trends**

In the years 2003–2009 a total of 671 publications were found on bisphosphonates and osteonecrosis of the jaw. Eight studies were published in 2010 with e-pub in 2009 and were listed in 2009. Since literature research was performed up to March 2010 and there was much more published after March, it would not have made sense to create a separate statistic for 2010. From 2003 there was a continuous rise in the number of publications per year, with the highest amount of publications in 2009 (Fig. 1). After 2006 there were over a hundred publications on the topic of BRONJ every year.

**Specification of journals**

Most publications (n = 179; 26.7%) appeared in general dental journals with 123 publications in journals of dental associations,
In oral medicine, nine in implantology, and one in endodontics (Fig. 2). 20.1% of all publications \((n = 135)\) appeared in oral and maxillofacial surgery journals. 122 were published in oral and craniomaxillofacial surgery, seven in head and neck surgery, four in otolaryngology and two in laser surgery journals. 19.1% of all publications \((n = 128)\) appeared in general medical journals with 88 papers in journals of medical associations and one in public health. 13.0% of the papers \((n = 82)\) were published in journals of internal medicine \((n = 9)\), haematology \((n = 18)\), rheumatology \((n = 17)\), bone and mineral research \((n = 14)\), endocrinology and metabolism \((n = 10)\), nutrition and metabolic therapy \((n = 5)\), arthritis \((n = 4)\), osteoporosis \((n = 4)\) and one in clinical nutrition and metabolic care. Publications in other journals \((n = 58)\) make up 3.6% of all publications, with 11 papers in pharmacology journals, 9 in radiology, 6 in urology and nephrology journals, 5 in orthopaedic, 5 in biochemistry and cell biology, 4 in pathology and neurology, 4 in journals of climacterics and menopause, 3 in toxicology and 2 in gynaecology, gerontology and neuroradiology.

**Classification of evidence**

A total of 176 publications out of 671 could be classified (Table 2).

Only one study with evidence level Ia was found. This study by Mauri et al. is a meta-analysis of several randomized controlled clinical trials published in 2009. 30

Eight publications showed evidence level Ib, which were the results of at least one randomized controlled clinical trial. One study by Jeffcoat et al. represents an update of a trial from the year 2006. 32 This article had lower evidence because it included a non-randomized study.

Nine non-randomized studies had a level of evidence grade IIa. The group with evidence Ib comprised 25 studies. These were quasi-experimental studies, such as time series analyses without randomization.

A total of 101 publications with evidence III were found. These were the results of descriptive studies such as cohort studies or case-control studies.

The 32 publications with evidence IV were reports by respected authorities and their clinical experience or panels of experts from several medical organizations.

**Incidence of BRONJ according to the type of bisphosphonate application**

**Intravenous application**

The results were extracted from studies focusing on the incidence of BRONJ as well as on the therapy of BRONJ. A total of 47 studies revealed information on the incidence of BRONJ after intravenous application (Table 3). The mean incidence over all the reviewed publications was 7% with a high variation from 0.0% published by Lyles et al., Bianchi et al. and Malmgren et al. 2008 up to 27.5% in a study by Boonyapakorn et al. 34,55–57 Besides a high variance in incidence, the studies showed a high variance in design. 30 studies (63.7%) were retrospective studies, 14 (29.7%) were prospective, two studies (4.5%) were letters to the editors and one (2.1%) study was a review. The median duration of the studies showed wide differences, ranging from 5 months according to Vahtsevanos et al. to 75 months in a study published by Kanat et al. (Table 3). 106,165

**Oral application**

A total of 9 studies were reviewed in which information on the incidence after oral bisphosphonate application was directly

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**Table 2**

Publications listed according to the year of appearance and grade of evidence.\(^{170}\)

<table>
<thead>
<tr>
<th>Year</th>
<th>Level Ia</th>
<th>Level Ib</th>
<th>Level IIa</th>
<th>Level III</th>
<th>Level IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>168</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td></td>
<td>10,15</td>
<td></td>
<td></td>
<td>168</td>
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<tr>
<td>2005</td>
<td></td>
<td>73–78</td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>2006</td>
<td>33,34</td>
<td>48,50</td>
<td>51–53</td>
<td>12,93–118</td>
<td>9,17,26,169–174</td>
</tr>
<tr>
<td>2007</td>
<td>35–37</td>
<td>54–60</td>
<td>119–141</td>
<td></td>
<td>16,18,22,28,102,175,176</td>
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<td></td>
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<td>26,27,180–186</td>
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</tbody>
</table>

* Published in the year 2010 but epub ahead in 2009.
retrievable or retrospectively calculated by the authors from the published data (Table 4). The overall incidence of BRONJ after oral bisphosphonate application was 0.12%, ranging from 0.0% in a study by Black et al., Jeffcoat et al., Fugazotto et al., Murad et al. and Bianchi et al. to 4.3% published by Seghizadeh et al. (Table 4). Three, twenty-five studies (32, 33, 55, 119, 159) were prospective studies (55%). The mean duration of the studies ranged from 24 months in Jeffcoat et al. and Mavrokokki et al. up to >60 months in a study by Black et al. Three, twenty-five studies (32, 33, 55, 119, 159) were prospective studies (55%).

### Treatment outcomes

Table 5 and 6 show different treatment concepts for 403 BRONJ patients based on 15 studies. 123 patients had conservative treatment (Table 5), 255 patients had surgical treatment (Table 6) and the remaining 25 patients had combinations of both. 388 out of the 403 patients were given antibiotics. The combination of radical surgery and antibiotics was found in the treatment of 240 patients (59.7%). 141 (58.8%) of them had healing of the lesion. 47 (19.6%) of them had an improvement with...
resolution of their clinical symptoms. 10 patients (4.2%) had refractory or new BRONJ.

The combination of conservative treatment with administration of antibiotics was found in 103 patients. 66 (64.1%) of these patients had healing of their lesions. Six patients (5.8%) showed an improvement with resolution of their clinical symptoms. Eight patients (7.8%) had refractory or new BRONJ.

In 27 patients antibiotics only were administered. In 18 (66.7%) of these patients an improvement with resolution of their clinical symptoms was found.

Other treatment concepts included ND:YAG laser stimulation or pulse application in 14 patients, once in combination with antibiotic therapy in six patients and once in combination with surgical wound débridement in eight patients. Half of the first group and the whole of the second group of these patients had healing of their lesions.

Discussion

Numerous studies on BRONJ have been published in the last few years. However, there has not been any study evaluating the level of evidence of these published data according to the classification of Shekelle et al. Additionally there has not been any work evaluating and classifying the number of publications according to the different medical or dental fields, e.g. journals. Since the first publication on the topic “BRONJ”, a constant
increase in terms of the numerical trend can be seen. In 2010 there were already more than 200 publications listed in PubMed, and more than 150 in December 2011.

In accordance with the statement of the American Society for Bone and Mineral Research (ASBMR), it is very difficult to compare the studies because of the heterogeneity of the referred methods. Due to this lack of uniformity the information is not always compatible.

Although most of the bisphosphonates are prescribed by internists, haematologists, urologists, and gynaecologists, most of the literature on BRONJ is published in journals of general dentistry, and oral and cranio-maxillofacial surgery. This is not surprising since patients suffering from BRONJ are referred to dentists or oral and maxillofacial surgeons for treatment. However, it was interesting to find only two publications in gynaecology journals and six in urology and nephrology. A much higher number of publications would have been expected in these medical fields. Obviously BRONJ seems to be of rather low interest in these fields, which contrasts with the severity and incidence of this reported effect of intravenous bisphosphonate therapy.

The general incidence of BRONJ is difficult to determine because of variables such as type, dosage, duration of the bisphosphonate treatment, disease and status of disease, age, other diseases and medications. Generally, the incidence of BRONJ is lower for oral than for intravenous bisphosphonate application. Oral bisphosphonates are mostly used for the treatment of osteoporosis or Paget’s disease. In contrast to this, intravenous BP application is used for the treatment of malignancies, thus being related to a completely different status of health and concurrent medication of patients. In all studies focusing on oral bisphosphonate application with osteoporotic dosage, the BRONJ ratio in number of patients is 46/36,951 and the incidence of BRONJ is 0.12%.

Due to this lack of uniformity the information is not always compatible.

Math et al. in which conservative treatment was also performed in stage II and III patients. Both studies showed worse outcomes for conservative treatment in terms of worse or refractory healing and resolution of pain when compared to all other studies involving conservative treatment of level I necrosis. We conclude that conservative treatment might only lead to complete healing in stage I patients. The present review shows that surgical procedure in terms of exploration and resection of necrotic bone results in successful healing of 60%. Although complete healing was not achievable in 20%, patients showed at least a relief of pain. With regard to these results, almost 80% of the patients had a direct benefit related to surgical intervention. Only 3% showed worse outcomes with refractory healing and resolution of pain after surgery and 16.5% were either lost to follow-up or showed the same stage. Most studies with surgical procedure included patients with high stages of necrosis. With regard to the poor conditions associated with high stages of necrosis in these groups, it might be concluded that surgical therapy in cases with low-grade necrosis might result in even higher success rates than if conservative treatment is performed. Evaluating the results of this review and taking our own experiences into account, we recommend conservative treatment as initial treatment for pain control and chronicity of acute inflammatory signs before surgical treatment in any stage of BRONJ. Surgery, however, seems to be inevitable in most of the cases where complete and successful healing is the aim. Surgery may be avoided if complete healing appears during the initial phase of pain control, local disinfection (by mouth rinse or topical application of disinfectant paste) and administration of antibiotics. This, however, seems to be confined to a rather rare number of cases.

The benefit of using ND:YAG laser stimulation or pulse application has not yet been proved.
As yet there are no studies which have evaluated the level of evidence for trials published before 2010. The results of the present study show that the overall level of evidence concerning the incidence and treatment strategies for BRONJ is rather low. The high number of publications reflects the increasing number of patients with BRONJ. BRONJ may be expected to gain more and more importance in the future. With regard to these aspects, there is a need for additional studies to achieve more evidence concerning the pathomechanism, the incidence, treatment outcomes as well as strategies for the therapy and prevention of BRONJ.

Conflict of interest statement
None declared.

We hereby disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) our work.

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