Bisphosphonates and osteonecrosis of the jaw: cause and effect or a post hoc fallacy?

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Received 4 September 2005; revised 4 December 2005; accepted 9 December 2005

Background: An increasing amount of reports are being published suggesting a relationship between the use of bisphosphonates (BPs) and the development of osteonecrosis of the jaw (ONJ). We reviewed the currently available evidence and explore the potential mechanisms of action based on the known effects of the concerned BP.

Design: The MEDLine, Current Contents and Science Citation Index Expanded databases were queried and the results augmented by analyzing cited references and recent congress proceedings.

Results: 22 papers were included detailing 225 patients, all based on retrospective chart review without control groups. The prevalence of ONJ was estimated at 1.5%. The involved BPs were pamidronate, zoledronic acid, alendronate and risedronate, all potent nitrogen-containing agents. The most common symptom was pain (81.7%), although 12.2% of cases were asymptomatic. In 69.3% of patients ONJ was preceded by a dental extraction. At the time of diagnosis, 74.5% of patients were receiving chemotherapy and in 38.2% of cases corticosteroids were administered. Although various conservative and surgical treatment modalities were reported, residual sites of ONJ persisted in 72.5% of cases.

Conclusion: Although not enough evidence is available to prove a causal link, it seems that under specific circumstances local defenses can become overwhelmed resulting in ONJ.

Key words: bisphosphonates, jaw, osteonecrosis

Introduction

The bisphosphonates have been studied intensively in an attempt to elucidate the exact mechanism of osteoclast inhibition and other potentially anti-neoplastic properties [1, 2]. The uncertainty surrounding the involved biomolecular pathways has however not delayed their introduction in daily clinical practice. In fact, they have proven to be very useful in the treatment of conditions characterized by excessive bone resorption including osteoporosis, Paget’s disease and hypercalcemia of any cause [3]. In cancer patients in particular, the role of bisphosphonates in the prevention of skeletal related events has been well established and these drugs have been incorporated in the treatment guidelines for a number of common malignancies [4–6].

Although serious side-effects have been reported, including acute renal failure after intravenous administration or gastrointestinal toxicities such as esophagitis when orally, these drugs are in general well tolerated [7]. Undoubtedly this mild side-effect profile has contributed to the spectacular increase in the use of bisphosphonates over the past decade.

However, a number of case series have recently been published documenting patients who developed osteonecrosis of the jaw (ONJ) apparently all after receiving bisphosphonate therapy. This rare disorder has been associated with chemotherapy, but was not frequently reported prior to 2003 [8]. At the moment it is unclear whether this association is based on coincidence or if a true causal relationship exists.

This paper reviews the currently available literature and examines the arguments pointing towards causality. Additionally, the in vivo and in vitro effects of the concerned bisphosphonates are summarized in order to present a number of potential mechanisms that could be responsible for ONJ.

Methods

The following databases were queried using a combination of the search terms listed in Table 1: MEDLINE (1966 – July 2005, SilverPlatter MEDLINE®, National Library of Medicine), Current Contents (1997 – July 2005, CU Search®, The Institute for Scientific Information) and Science Citation Index Expanded (1972 – July 2005, Web of Science®, The Thomson Corporation). All search results were scanned for relevancy and the original publication was retrieved when appropriate. Additionally, to augment the computerized literature search, the reference lists of each identified paper...
were manually reviewed to identify other works of interest. Finally, the websites of the American Hematological Society (http://www.hematology.org, last accessed 27/05/2005), American Society of Clinical Oncology (http://www.asco.org, last accessed 27/05/2005), the International Myeloma Foundation (http://www.myeloma.org, last accessed 27/05/2005) and The San Antonio Breast Cancer Symposium (http://www.sabcs.org, last accessed 27/05/2005) were visited to search for abstracts and congress proceedings.

Each paper was subsequently analyzed to extract a set of relevant clinical parameters (Table 2). A patient was eligible for inclusion when treatment with a bisphosphonate was documented prior to the discovery of ONJ and when the diagnosis, whether based on clinical or histological grounds, was made by a qualified physician or dentist. After data extraction, summary measures were calculated with 95% confidence intervals for the investigated variables using traditional techniques for pooling means and standard deviations [9]. Whenever there was ambiguity surrounding any of the published cases an attempt was made to contact the corresponding author to resolve this issue.

**results**

A total of 32 relevant references were identified and retrieved for analysis. These included 22 papers reporting individual cases and were published as a full article (n = 1), a case report (n = 7), a letter to the editor (n = 6) or an abstract from congress proceedings (n = 8) (Table 3) [10–31]. Four case series were found to include individuals presented earlier in abstracts and were analyzed accordingly [10, 13, 14, 16, 19, 23, 26, 28]. Additionally, five letters, two editorials and one commentary were identified, all commenting on and citing previously published case series [32–39].

Furthermore, an online survey was found from the International Myeloma Foundation (IMF) asking its members to report if they had been diagnosed with ONJ or suffered from symptoms suspicious for osteonecrosis [40, 41]. Although such surveys are fraught with epidemiological danger related to reliability, validity, recruitment and reporting bias they can be a useful instrument to rapidly screen a particular community for the occurrence of specific symptoms. Because of the previously described concerns the patients of this study were not included for analysis.

Finally, one letter was identified describing 3 patients with ONJ allegedly caused by chemotherapy. However, in retrospect the author suggests that based on the recently published data the reported cases were probably induced by bisphosphonates [42].

The quality of the published reports was generally moderate, due to the incomplete reporting of useful parameters or the lack of sufficient descriptive measures. In respect of the variables defined in Table 2, the median completeness of the reported information for every patient was 78.6% (range 28.6–88.1%). All reports were observational and retrospective in nature without control groups, citing chart review as the source for the published data.

In total, data describing 225 individual patients was extracted and included for analysis. Only one paper described the size of the original population of oncological patients in which the cases occurred and reported a prevalence of osteonecrosis of 1.5% [17]. General patient characteristics were provided for 162 (72.0%) patients consisting of 52 males and 110 females with a mean age of 65.3 (SD 11.3, 95%-CI 63.5–67.1) years. The indication for bisphosphonate use was specified in 210 (93.3%) cases and included disseminated cancer in 198 (94.3%), osteoporosis in 9 (4.3%) and Paget’s disease in 3 (1.4%) patients. Multiple myeloma was the most common reported malignancy (n = 97), followed by breast cancer (n = 89), prostate cancer (n = 6), leukemia (n = 1), sarcoma (n = 1), lung cancer (n = 1), ovarian cancer (n = 1), both ovarian and breast cancer (n = 1), and both prostate cancer and lymphoma (n = 1). The malignant involvement of the skeleton was verified in 131 (58.2%) patients and all were found to have metastases to the bone.

For all but 1 (0.4%) patient the history of prescribed bisphosphonates at the time of diagnosis of ONJ was specified, with pamidronate and zoledronic acid being used most frequently followed by alendronate and risendronate (Figure 1). The duration of bisphosphonate therapy could only be reconstructed for 60 (26.7%) individuals (Figure 2), although summary measures were available for 100 (44.4%) cases, resulting in a mean length of treatment of 29.5 (SD 24.0, 95%-CI 23.9–35.2) months.

The most common presenting symptom of ONJ was pain (n = 94), followed by purulent discharge (n = 10), oroantral fistula

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**Table 1.** The following terms were used in different combinations and with logical operators to query the specified databases (plural forms are not listed separately)

<table>
<thead>
<tr>
<th>Osteonecrosis</th>
<th>Bisphosphonate</th>
<th>Alendronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avascular necrosis</td>
<td>Diphosphonate</td>
<td>Pamidronate</td>
</tr>
<tr>
<td>Bone necrosis</td>
<td>Etidronate</td>
<td>Zoledronate</td>
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<tr>
<td>Osteomyelitis</td>
<td>Clodronate</td>
<td>Zoledronic acid</td>
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<tr>
<td>Mandible</td>
<td>Tiludronate</td>
<td>Risedronate</td>
</tr>
<tr>
<td>Maxilla</td>
<td>Zometra</td>
<td>Ibandronate</td>
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<tr>
<td>Jaw</td>
<td>Aredia</td>
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</tbody>
</table>

**Table 2.** To reconstruct the individual characteristics of each reported case, the following items were retrieved from the included reports for every patient

1. Age
2. Sex
3. Disease for which bisphosphonate therapy was initiated
4. Which bisphosphonate was administered?
5. Duration of bisphosphonate therapy
6 What were the presenting symptoms?
7. Location of osteonecrosis (maxilla, mandible or both)
8. Was osteonecrosis preceded by dental extraction?
9. Which therapy was initiated?
10. What was the final outcome after therapy?
11. Did the patient take corticosteroids?
12. Type of malignancy?
13. Were metastases to the bones present?
14. Was chemotherapy administered concomitantly and if so which type?
15. Did the patient ever receive radiotherapy to the involved region?
16. Was a biopsy performed to exclude the presence of malignancy?
Table 3. Overview of available evidence documenting patients with osteonecrosis of the jaw

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Disease (n)</th>
<th>Involved bisphosphonate</th>
<th>Location (n)</th>
<th>Active treatment (n)</th>
<th>Number of cases with (%)</th>
<th>Dental extraction</th>
<th>Local radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bagan et al. [25]</td>
<td>10</td>
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<td>Pamidronate</td>
<td>Mandible (5)</td>
<td>Steroids (4) Thalidomide (2) CMF (1) FEC (7) Taxanes (2)</td>
<td>7 (70.0)</td>
<td>–</td>
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<td></td>
<td></td>
<td></td>
<td>Zoledronic acid</td>
<td>Mandible and maxilla (5)</td>
<td>Hormonal therapy (7) Steroids (2)</td>
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<tr>
<td>Carter et al. [10, 26]</td>
<td>5</td>
<td>Multiple myeloma (2) Paget’s disease (3)</td>
<td>Alendronate</td>
<td>Maxilla (4)</td>
<td>Steroids (15)</td>
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<td>Pamidronate</td>
<td>Mandible (15)</td>
<td>Steroids (15)</td>
<td>13 (56.5)</td>
<td>1 (4.3)</td>
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<td>Pamidronate</td>
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<td>Steroids (7)</td>
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<td>2 (28.6)</td>
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<td>0 (0)</td>
<td>0 (0)</td>
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<tr>
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<td>FEC (1)</td>
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<td>Pamidronate</td>
<td>Maxilla (1)</td>
<td>Capcitabine (1)</td>
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<td>Migliorati et al. [13, 28]</td>
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<td>Breast cancer (10) Multiple myeloma (3) Prostate cancer (1) Osteoporosis (1) Ovarian cancer (1) Ovarian and breast cancer (1) Prostate cancer and lymphoma (1)</td>
<td>Zoledronic acid</td>
<td>Maxilla (2) Mandible and maxilla (1)</td>
<td>Hormonal therapy (8) Thalidomide (1) Melphalan (1) Cyclophosphamide (2) Doxorubicin (7) VAD (4) Vinca alkaloids (1) Cisplatin (1) Taxanes (3) Capecitabine (1)</td>
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<td>Involved bisphosphonate</td>
<td>Location (n)</td>
<td>Active treatment (n)</td>
<td>Number of cases with (%)</td>
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<td>Dental extraction</td>
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<td>4 (40)</td>
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<td>14</td>
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<td>Vanucchi et al. [29]</td>
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<td>Zoledronic acid</td>
<td>Mandible (1)</td>
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<td>Wang et al. [15, 42]</td>
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<td>Pamidronate</td>
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<td>Taxanes (3)</td>
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<tr>
<td>Zarychanski et al. [24]</td>
<td>4</td>
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<td>Pamidronate</td>
<td>Mandible (4)</td>
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</table>

CMF: Cyclophosphamide, methotrexate and fluorouracil; FEC: fluorouracil, epirubicin and cyclophosphamide; NOS: Not otherwise specified; VAD: Vincristine, doxorubicin and dexamethasone.
n = 7), swelling (n = 3) and fever (n = 1), with data available for 115 (51.1%) patients. In 14 (12.2%) other patients ONJ was asymptomatic and was found during routine check-up.

Fourteen reports, corresponding to 176 (78.2%) cases, provided information on the history of dental extractions at the site of osteonecrosis and documented such a procedure in 122 (69.3%) patients. The location was detailed in 179 (79.6%) patients and most frequently occurred at the mandible (n = 119), followed by the maxilla (n = 48) and in 12 patients both were affected.

To rule out malignancy as the cause of ONJ a biopsy of the affected region was performed in a total of 114 (50.7%) patients, none of which showed the presence of neoplastic disease. Only eight (4.4%) patients had previously undergone radiotherapy to the affected region with respect to the 182 (80.9%) cases for whom data was reported.

The active treatment at the time of diagnosis was reported for 165 (73.3%) patients. Out of these, 123 (74.5%) patients were treated with chemotherapy although the specific cytotoxic agents were only detailed for 43 cases: paclitaxel or docetaxel (n = 9); fluorouracil, epirubicin, and cyclophosphamide (n = 8); doxorubicin (n = 7); melphalan (n = 6); vincristine, doxorubicin, and dexamethasone (n = 6); capecitabine (n = 2); cyclophosphamide (n = 2); cisplatin (n = 1); cyclophosphamide, methotrexate, and fluorouracil (n = 1) and vinorelbine (n = 1).

Fifteen (9.1%) patients with breast cancer received hormonal therapy whereas thalidomide was used in 8 (4.8%) cases with multiple myeloma. In 63 (38.2%) patients the therapeutic regimen also included corticosteroids.

The treatment initiated for ONJ was detailed for 177 (78.7%) patients with each patient undergoing an average of 1.8 (SD 0.9, 95%-CI 1.5–2.1) therapeutic measures. Conservative management consisted of antibiotics (n = 82), chlorhexidine rinse (n = 52), narcotic medication (n = 9), discontinuation of bisphosphonates (n = 9), hyperbaric oxygen therapy (n = 9) or was not otherwise specified in two patients. Surgical modalities included local debridement (n = 70), sequestrectomy (n = 60) or partial removal of the affected bone (n = 25).

The final outcome after treatment was only reported for 40 cases with healing of the lesions occurring in 11 (27.5%) patients and residual sites of necrosis remaining in 29 (72.5%).

**review of the effects of bisphosphonates**

The bisphosphonates are divided into two subclasses based on whether or not one of the side chains contains a nitrogen atom (Figure 1). The less potent non-nitrogen containing bisphosphonates (e.g. etidronate, clodronate, tiludronate) are believed to induce osteoclast cell-death by the formation of cytotoxic metabolites of adenosine triphosphate (ATP)
that accumulate and interfere with intracellular metabolic enzymes [1].

The potent nitrogen-containing bisphosphonates (e.g. pamidronate, alendronate, risedronate, ibandronate, zoledronic acid) on the other hand inhibit the mevalonate pathway. By blocking the enzyme farnesyl diphosphate synthase an intracellular shortage is created of amongst others geranylgeranyl diphosphate and farnesyl diphosphate, both required for the post-translational lipid modification (prenylation) of small signaling proteins with GTPase activity. The resulting dysfunction hampers the regulation of osteoclast morphology and activity, leading to poor cell functioning and apoptosis [43].

Other researchers have focused on the effects of the nitrogen-containing bisphosphonates on tumor cells. In vitro experiments have confirmed that they can inhibit the adhesion of neoplastic cells to bone, reduce the ability to invade artificial membranes and slow down cell migration, all at doses that are unable to cause direct cytotoxicity or induce apoptosis [2].

The nitrogen-containing bisphosphonates can in vitro induce apoptosis and inhibit cell growth of malignant cells, again by disrupting the mevalonate pathway. Furthermore, all bisphosphonates can in vitro inhibit certain matrix metalloproteinases, a family of zinc-dependent enzymes that participate in normal wound repair and are used by tumor cells to facilitate invasion into surrounding tissues [44].

In animal models the bisphosphonates also disrupt the intricate relationship that exists between cancer cells and osteoclasts, by preventing the release of transforming growth factor-beta (TGF-β) and insulin-like growth factor-I (IGF-I) [45].

Additionally, it has been confirmed in animal models that zoledronic acid, a nitrogen-containing bisphosphonate, can inhibit angiogenesis by reducing the sprouting of new vessels and suppressing endothelial cell proliferation [46]. Similarly, a reduction in the amount of circulating vascular endothelial growth factor (VEGF) has been demonstrated in humans after the administration of zoledronic acid [47].

Finally, some patients develop self-limiting acute-phase reactions after the administration of bisphosphonates resulting in mild flu-like symptoms, probably caused by the release of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) [7].

How all these findings relate to the daily practice remains unclear and further in vitro and in vivo research is necessary to explore these issues. However, from the above it is clear that the bisphosphonates have a broad spectrum of effects that go beyond the simple inhibition of bone resorption.

discussion

The introduction of the potent bisphosphonates has been a blessing for cancer patients with disseminated disease to the bone. However, evidence is accumulating linking their use with the occurrence of painful osteonecrosis of the jaw. We identified 225 such cases that have been documented in the medical literature in mainly multiple myeloma and breast cancer patients.

At first the bisphosphonates seem an unlikely culprit, as pamidronate and zoledronic acid have been used in almost 2.5 million patients worldwide to improve bone architecture and mineralization [32, 43]. Furthermore, cases with avascular necrosis of the femur have been successfully treated with alendronate and in vivo research suggests that they can block the resorption of necrotic bone during revascularization, preventing further collapse [48, 49].

Because bisphosphonates are so ubiquitous, many other confounders can simulate causality as the treatments for multiple myeloma and breast cancer have been expanded and intensified over the last decade.

Indeed, local radiotherapy, chemotherapy and chronic osteomyelitis have all been identified as a cause of ONJ [15]. Likewise, it is well known that the long-term use of corticosteroids and allogeneic stem-cell transplantation (SCT) can lead to avascular necrosis of the femoral head, both frequently used in the treatment of multiple myeloma [50, 51]. Although the number of patients presenting with ONJ seems to be increasing, the exact prevalence in cancer patients remains unknown [19, 21]. Kut and colleagues report a prevalence of ONJ amongst multiple myeloma patients of 1.5% [17].

Moreover, patients did not respond to traditional treatment modalities with lesions persisting in 72.5% of cases, suggesting a changing epidemiology.

The involved agents belong exclusively to the class of potent nitrogen-containing bisphosphonates and are mainly pamidronate and zoledronic acid and to a lesser extent alendronate and risedronate.

Only 8 (4.4%) out of 182 patients had received radiotherapy to the jaw which virtually excludes this modality as a possible confounder. Similarly, none of the 114 patients who underwent a biopsy of the affected site was found to have malignant involvement. In contrast, 74.5% of the cases were actively receiving chemotherapy and in 38.2% of patients steroids were administered and the influence of these agents should therefore be considered.

Historically, Hill and others have put forward a framework outlining the properties of a true causal association [52]. A temporal association should be present, where the exposure must precede the initial onset of symptoms and all currently published cases support such a relationship. The following four characteristics (consistency, strength of association, specificity and dose-response relationship) can only be established by studies with control groups where individual exposure can be linked to individual outcome. It is clear that at this time that data is lacking, precluding any definitive judgment on causality.

Finally, to support the biological plausibility of causality two questions should be answered: what are the etiological mechanisms of ONJ and to what extent can the bisphosphonates contribute to this process?

Research into the etiology of osteonecrosis of the hip has produced a concept of accumulative cell stress, where multiple stress factors overwhelm the osteocytes and damage their microenvironment, leading to a state where they are unable to recover from chronic damage and eventually die [33]. Applied to ONJ, a similar model can be hypothesized where bisphosphonates would contribute to a disturbed bone homeostasis by inhibition of osteoclast function. The disruption of the normal bone turnover and remodeling would cause the accumulation of non-vital osteocytes and microfractures [11].
The observation that a majority of patients (69.3%) underwent a dental extraction prior to the development of osteonecrosis seems to confirm the importance of trauma in the initiation of the disease. Animal research has indeed demonstrated the important role of osteoclasts in the healing of alveolar bone after dental extraction [54]. Moreover, the jaws are the only bones in the human body that come in frequent contact with the outside world and are subject to repeated microtrauma through the presence of teeth [11].

When local defenses are overwhelmed by infection, trauma or surgery various microorganisms can invade the underlying bone. Additionally, the inhibition of angiogenesis may aggravate this process by compromising the vascular supply of the healing tissue [28]. The recently introduced agents thalidomide and bortezomib, used in the therapy against multiple myeloma, block angiogenesis as well and could possibly contribute to the development of the disease [55]. Both a disrupted bone turnover and a critical vascular supply could affect the quality of bone during growth and healing, promoting the development of a nonhealing wound and osteonecrosis, leaving the lesion prone to infection that can progress to widespread osteomyelitis.

Finally, both hypocalcemia and hypophosphatemia have been documented in patients receiving bisphosphonate therapy [7]. The effect of these ion imbalances on the healing bone is currently unknown, but both might cause poor mineralization of newly formed osteoid. Although none of these observations prove a causal relationship, they do suggest that the bisphosphonates could potentially be involved in a complex interaction with numerous other effects resulting in ONJ (Figure 4).

In response to the published data, Novartis (East Hanover, NJ) has updated the package inserts of pamidronate (Aredia®) and zoledronic acid (Zometa®) to reflect the current concerns and has issued a document based on expert consensus detailing the diagnosis and treatment of osteonecrosis, as well as recommendations to prevent the condition [36].

Prior to the initiation of bisphosphonate therapy a thorough evaluation of the dental status should be performed to identify existing infections, compromised teeth and ill-fitting dentures. If bisphosphonate therapy can be delayed, preventive surgery to eliminate potential sites of infection should be performed. Otherwise, any elective jaw procedure requiring bone healing should be avoided.

Optimal dental health during treatment is essential and all patients should be informed of the importance of good oral hygiene. In addition, regular visual inspections by the treating oncologist and routine assessments by a dental specialist are warranted. Whenever treatment is necessary, the less invasive endodontic techniques with preservation of the dental root are favored with a possibly beneficial impact of antibiotic therapy. Interruption of bisphosphonate therapy can be considered in severe cases if the benefits outweigh the risk of skeletal related events, although no improvement was observed in the published cases [28]. Similarly, hyperbaric oxygen therapy has not been shown to be effective.

In conclusion, at the moment not enough data is available to prove a causal link between the use of bisphosphonates and osteonecrosis of the jaw. However, enough circumstantial evidence has been published to alert clinicians to be vigilant and encourage the meticulous reporting of every occurrence of osteonecrosis, a disease with a low prevalence but a potentially high impact.

Figure 4. Hypothetical mechanism of osteonecrosis induced by potent nitrogen-containing bisphosphonates. Through inhibition of osteoclast function (a) and angiogenesis (b) the regenerative capacity of the bone is impaired. After local trauma the non-healing wound can develop into osteonecrosis and is prone to surinfection by commensal flora (c) leading to osteomyelitis.

**References**