ELSEVIER

Bone xx (2008) xxx–xxx

BONE

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Review

Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis

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Received 24 October 2007; revised 19 December 2007; accepted 8 January 2008

Abstract

A potential side effect associated with bisphosphonates, a class of drugs used in the treatment of osteoporosis, Paget's disease and metastatic bone disease, is osteonecrosis of the jaw (ONJ). The incidence of ONJ in the general population is unknown; this rare condition also may occur in patients not receiving bisphosphonates. Case reports have discussed ONJ development in patients with multiple myeloma or metastatic breast cancer receiving bisphosphonates as palliation for bone metastases. These patients are also receiving chemotherapeutic agents that might impair the immune system and affect angiogenesis. The incidence or prevalence of ONJ in patients taking bisphosphonates for osteoporosis seems to be very rare. No causative relationship has been unequivocally demonstrated between ONJ and bisphosphonate therapy. A majority of ONJ occurs after tooth extraction. Furthermore, the underlying risk of developing ONJ may be increased in osteoporotic patients by comorbid diseases. Treatment for ONJ is generally conservative.

Keywords: Bisphosphonates; Osteoporosis; Osteonecrosis; Bone turnover; Metastases

Contents

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doi:10.1016/j.bone.2008.01.003

Introduction

Bisphosphonates are a class of drugs used in the treatment of osteoporosis, Paget's disease and metastatic bone disease. A potential side effect associated with bisphosphonates is osteonecrosis of the jaw (ONJ), a rare condition of unknown incidence in the general population that has also been known to occur in patients not receiving bisphosphonates.

Most publications in the literature relating to ONJ are based on empirical data and consensus. To date, little evidence-based data concerning ONJ are available, with the majority coming from the oncology setting. Few data are available from patients receiving bisphosphonate therapy for osteoporosis.

On 14th December, 2006, a Working Group meeting was convened in Geneva, Switzerland, by the European Society on Clinical and Economic Aspects of Osteoporosis and by the Foundation for Research on Osteoporosis and other Bone Diseases. The meeting focused on the impact of ONJ on the management of osteoporosis, and the outcomes from the meeting are presented in this paper.

Methods

An extensive literature search of various medical databases (e.g. Medline, Embase, Cochrane reviews) (keywords: bisphosphonates, cancer, malignancies, osteonecrosis, jaw, osteoporosis, adverse reactions) identified relevant papers published in English between January 1995 and July 2006. Key experts from various areas (i.e. orthopaedic surgery, dental and maxillofacial surgery, epidemiology, health economics, oral pathology, endocrinology, rheumatology, primary care and physical medicine and rehabilitation, together with representatives from industry) were identified based on this literature search and invited to a consensus experts meeting (funded by the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis [ESCEO]) to produce the current consensus document.

Definition of osteonecrosis of the jaw

A universally agreed definition for ONJ has not been established to date. Inevitably, the absence of a consensus definition has resulted in confusion with respect to what constitutes ONJ, and how to diagnose the condition. Marx and Stern first described ONJ associated with bisphosphonate use in 2002 [1]. The definition has continued to evolve and updated versions have been published, most recently by the American Dental Association [2] and by Ruggiero et al. [3]. The American Association of Oral and Maxillofacial Surgeons has also recently published a staging system for ONJ and corresponding treatment strategies for each stage [4]. An ASBMR multidisciplinary task force has recently extensively reviewed all published data issued recommendations [5]. Our Working Group endorsed the following definition for ONJ: "exposed bone in the mandible, maxilla or both that persists for at least 8 weeks, in the absence of previous radiation and of metastases in the jaws".

Epidemiology

During the past 3 years, a number of reports have discussed ONJ associated with the use of bisphosphonates. These case reports and case series describe patients with multiple myeloma or metastatic breast cancer receiving high doses intravenous bisphosphonates (primarily pamidronate and zoledronic acid) as adjunctive therapy. Only few of these reports discuss patients receiving oral bisphosphonates for the treatment of osteoporosis, Paget's disease or other skeletal disorders. In total, 12 papers have been identified that contain information on ONJ among patients receiving oral bisphosphonates [6–17]. Among these reports, 443 patients were identified with ONJ, with 50 receiving oral bisphosphonates for the treatment of osteoporosis or osteopenia, and 4 patients administered bisphosphonates for the treatment of Paget's disease (47 patients were taking alendronate, 5 risedronate and 2 were taking alendronate/risedronate). A case series involving 63 patients with osteomyelitis or ONJ reported that 7 of these patients were receiving oral bisphosphonates, without any history of malignant disease or exposure to chemotherapy.[16] Among several million patients with osteoporosis who have received oral bisphosphonate therapy, 50 ONJ events have been reported [18]. A German registry of ONJ has included more than 300 case reports, 189 of which have been evaluated to date [19]. Among these patients, only 3 were reported to be taking an oral bisphosphonate (alendronate).

Spontaneous reports of ONJ submitted to manufacturers of bisphosphonates indicate a reporting rate of approximately 1 event per 100,000 person–years of exposure for oral bisphosphonates [20]. These data should, however, be interpreted with caution, as these reports are not adjudicated and information required to classify these cases properly (e.g. medical history, concomitant medication, duration of exposure, etc.) is largely unavailable. More recently were reported 36 cases (with details in 26 of them) in Australia and 9 cases in Israel, most with oral alendronate [11,21]. In the former report, based on the estimated oral bisphosphonates sales, the frequency of ONJ could be as high as 1 event per 20,000 person–years. On the other hand, data from clinical trials of nitrogen-containing bisphosphonates analysing >60,000 patient–years of exposure found no evidence of ONJ among adverse events reported [20]. The type of study (retrospective vs prospective), inconsistent definition of ONJ, as well as a possible lack of adjudication can contribute to the large range of incidence estimates.

The limited data in the literature show that ONJ is much less common among patients administered oral bisphosphonates at the lower doses used for osteoporosis compared with patients who receive higher doses used for metastatic cancer. Underlying diseases, cancer therapy and possible impaired immunity further distinguish the latter patients from osteoporotic ones. Two cases of ONJ were reported as a complication of chemotherapy in 1982, hence before the era of bisphosphonates [22]. No conclusive data on the incidence or prevalence of ONJ in

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patients taking oral bisphosphonates for osteoporosis are available currently [18,23]. As a result, the degree of risk for ONJ in these patients is not certain and patients should therefore be monitored carefully [18]. Overall, no epidemiologic data on the incidence of ONJ in the general population are available. The fact that no specific diagnostic code for this condition has been produced limits the conduct of retrospective observational designs to assess this condition and its potential risk factors.

Pathogenesis

Several pathogenic mechanisms for ONJ have been proposed. One of the proposed mechanisms suggests that ONJ can be caused by bisphosphonate-induced low bone turnover, which leads to decreased blood flow, bone cell necrosis and apoptosis [16,24]. In conjunction with infection, this leads to the development of exposed, non-healing bone areas in the mouth [16,24], which may be thought of as an 'inside-out' process. However, the available data would suggest an 'outside-in' process as more likely, in which mucosal damage is the event preceding infection and subsequent bone necrosis. For example, a retrospective chart review of oncology patients (n=4000) treated with bisphosphonates (many of whom were also receiving other chemotherapeutic agents) suggested that mucosal damage was an important precipitating factor [25]. Tooth extractions were the dominating event preceding ONJ although other causes, such as periodontal disease, dental implant procedures, exostoses and ill-fitting dentures, were also reported as preceding ONJ.

Delayed epithelialization may result in exposed bone that, in the presence of oral bacteria, increases the risk of infection. Reid et al. have suggested that bisphosphonates may contribute to the pathogenesis of ONJ by being toxic to oral epithelium at pharmacologic concentrations [26]. A number of disease states (e.g. diabetes, human immunodeficiency virus infection) also predispose patients to becoming immunocompromised, which results in delayed healing and reduced ability to combat opportunistic infections. Therapy with steroids and cytostatic agents can delay wound healing, and interfere with wound epithelialization. The combination of compromised immunity and medications which can affect wound healing suggests that a multifactorial model is required to explain the pathogenesis of ONJ. In contrast, bisphosphonates have also been shown to stimulate gammadelta T cells, potentially contributing to cytotoxicity against tumor cells [27].

Alterations in angiogenesis

Osteonecrosis is reported most commonly in the hip or knee, and is not associated with infection at these sites. More accurately, it is termed avascular (or aseptic) necrosis and results from an interruption or compromise of the blood supply as a result of trauma, coagulopathy or corticosteroids. However, no case of ONJ has been reported in these disorders. Furthermore, there is no evidence to suggest that ONJ is a form of avascular necrosis since bacteria are always present.

Recently, several publications using *in vitro* or animal models have reported the possibility of angiogenesis inhibition by bisphosphonates [28–31]. This effect appears to be mediated primarily through inhibition of vascular endothelial growth factor and other angiogenic factors, which may be an underlying mechanism of ONJ. In contrast, in normal bone, zoledronic acid appears to have no inhibitory effect on angiogenesis-dependent processes [29–35], and data from an animal model have also shown that strong inhibition of bone resorption by bisphosphonate did not affect angiogenesis [33,36].

Alterations in bone turnover

Studies in animals and humans have consistently shown the effectiveness of bisphosphonates in decreasing the rate at which bone is remodeled [37]. However, in animal models of periodontal disease, bisphosphonate treatment is not associated with ONJ, despite interventions such as tooth ligation and inoculation of pathogenic bacteria [34–42]. The few published histological studies of ONJ [42–44] show vital cells and bone in more than half the patients, which suggests a lack of necrosis; however, it is unclear how representative such biopsies are. Further evidence against a key role for low bone turnover in the pathogenesis of ONJ is the pronounced uptake of bone-seeking isotopes on scintigraphic imaging of ONJ lesions [23,45]. Low uptake of isotope has been reported only in a few cases of late-stage ONJ [23].

Infection

Infection is a dominating component of ONJ and a pronounced overlap between jaw osteomyelitis and osteonecrosis exists. The background risk of jaw osteomyelitis is 4 events per 100,000 people, which is similar to the prevalence rates cited in several studies on nononcology ONJ. The histological studies on ONJ in the literature have all shown pronounced inflammatory changes. Specific staining for bacteria typically reveals *Actinomyces* [43], although this common

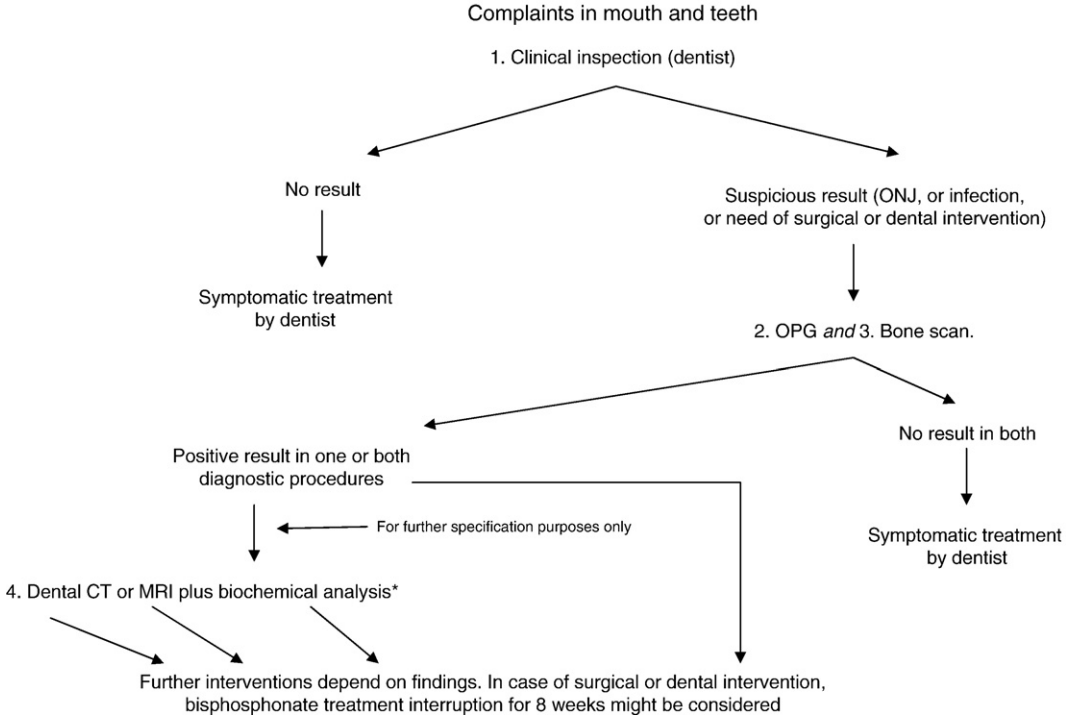

Fig. 1. Management algorithm for patients under bisphosphonate therapy. *Inflammation, bone turnover marker, blood cell count. ONJ, osteonecrosis of the jaw; OPG, orthopantomography; CT, computed tomography; MRI, magnetic resonance imaging.

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oral organism may be found as a consequence of the lesion rather than as an initiating factor. Bacterial analysis of ONJ is limited, however, and more studies are needed to determine whether anaerobic bacteria, such as those involved in periodontal disease, are concerned. Indeed, a large retrospective chart review has shown that a significant proportion of patients with ONJ have periodontal disease, which suggests these bacteria may indeed play a role [25]. On the other hand, bisphosphonates have shown to favorably influence the outcome of periodontal disease [46]. The function of infection in the pathogenesis of ONJ is further supported by reports of ONJ lesions improving after antibiotic treatment.

In summary, ONJ could be viewed as an alteration of normal wound healing in which "delayed" epithelial closure of an opening in the oral mucosa leads to an infection and subsequent necrosis of the bone. Multiple factors, including the patient's immunocompetence and the use of drugs (bisphosphonates, steroids) which impair wound closure may contribute to the pathogenesis.

Risk factors for osteonecrosis of the jaw development

To date, no clinical studies have systematically investigated risk factors for the development of ONJ in osteoporotic patients treated with oral bisphosphonates, which may possibly be a result of the low incidence of the condition. Thus, risk factors for this patient group have not been identified and remain speculative. It has been suggested that the underlying risk of developing ONJ may be increased in patients with osteoporosis and comorbid diseases such as rheumatoid arthritis or diabetes [9]. Further risk factor may be the cumulative exposure. Reminiscent to risk factors present in cancer patients treated with IV bisphosphonates, extrapolation to the osteoporosis setting [10] would include invasive oral treatments involving bone exposure (e.g. tooth extraction, subgingival curettage, periapical and periodontal surgery), trauma where bone is exposed to the oral microflora and poor oral hygiene. In osteoporosis patients treated with bisphosphonates, high cumulative doses administered over a long time period may be a risk for an increased incidence of exposed bone. This was observed in 3 patients receiving alendronate in a case series of 119 patients [10].

Radiologic assessment of osteonecrosis of the jaw

Osteonecrosis of the jaw is characterized by exposed bone in the maxillofacial area (which can occur after dental intervention or spontaneously) which fails to heal after 8 weeks of appropriate care (AAMOS criteria). For accurate assessment, bone morphology, soft tissue (gingiva) and bone function require examination using various scanning techniques (Fig. 1).

Assessment of bone function (metabolic activity)

Bone scintigraphy. A useful screening tool for detecting local bone remodeling/modeling activity is bone scintigraphy with Tc-99 methylene diphosphonate (MDP), which has high sensitivity but low specificity [47]. This technique aims to detect high bone turnover sites.

Positron emission tomography. Positron emission tomography with 2-(fluorine-18)-fluoro-2-deoxy-D-glucose (FDG) is capable of noninvasively detecting osteomyelitis (acute and chronic) with a high degree of accuracy. Inflammatory cells, such as neutrophils and activated macrophages, present in areas of acute or chronic inflammation take up FDG as a result of increased glycolytic activity [48–50], and accumulation of FDG in this way is a useful indicator of inflammatory processes [51]. Indeed, data from clinical studies investigating FDG for the early diagnosis of avascular necrosis of the femoral head after fracture of the femoral neck [52,53] showed a decreased uptake of the radionuclide in femoral heads, which were subsequently shown to be necrotic. With time, radionuclide uptake increased, which was attributed to revascularization and repair.

Assessment of bone morphology (non-invasive imaging)

Panoramic radiography. Panoramic radiographs (orthopantomography [OPG]) are routinely used in clinical practice. They are widely available, time efficient, and show the complete oral cavity on a single view. Radiography cannot adequately distinguish between osteonecrosis and metastatic osteoblastic lesions, but is useful when a combination of osteolysis and osteosclerosis is present (osteosclerosis is found in chronic osteomyelitis). Orthopantomography detects woven bone formations with periosteal thickening and marrow fibrosis, which cause the local bone area to increase in density. Typically, necrotic bone is characterized by a sequestrum positioned within pus or in the medullary cavity.

Disadvantages of OPG include the limited two-dimensional image. Moreover, the image quality may render difficult differentiating the margins between necrotic and healthy bone, with the result that early lesions can be missed. However, consensus suggests conventional radiographs should be used first-line as part of routine radiologic investigation [18].

Dental computed tomography. Computed tomography (CT) accurately detects alterations inside the bone, periosteal reactions and soft tissue alterations. CT avoids image distortions, such as those seen with OPG images, and provides excellent topographic anatomic illustration of the organ structure and pathologic findings. In patients with ONJ, CT can diagnose osteolytic and osteosclerotic regions, depending on the stage of the disease. More dense bone characterizes the necrotic area and more lytic areas illustrate the infected regions with pus and soft tissue swelling. The differentiation between malignant metastatic osteolysis and benign osteolysis may be difficult with CT.

Cone beam computed tomography. An alternative to CT, cone beam CT (CBCT) has gained increased acceptance as a three dimensional imaging modality [53,54], particularly in the maxillofacial bone area [55,56]. This is a relatively new technique that uses lower radiation dosages, and has a higher spatial resolution than conventional CT, providing improved image quality (especially for cancellous bone) [57,58]. Although discrimination of soft tissue may be limited as a result of a low contrast resolution, CBCT can provide detailed information about cortical thickness and integrity, marrow involvement, irregularities following tooth extraction, and cancellous bone density. CBCT is optimized for planning the placement of oral implants but not for diagnosis of ONJ.

Magnetic resonance imaging. Magnetic resonance imaging (MRI) of the jaw was used for identifying conditions related to the mandibular joint only, but modern techniques enable imaging of the bone marrow to illustrate the entire mandibula and maxilla, teeth, dental pulp, and even the mandibular canal. In patients with complicating clinical factors, fat-suppressed contrast-enhanced T1-weighted MRI has been shown to be significantly more sensitive than scintigraphy and significantly more specific than non-enhanced MRI or scintigraphy in diagnosing osteomyelitis [59].

Recommended assessment procedure for osteonecrosis of the jaw

The diagnosis of ONJ is made clinically if an oral lesion with exposed bone persists for more than 8 weeks. Lesions in patients who have had radiation therapy to the head and neck, or who have malignant disease within the jaw should be excluded from the diagnosis of ONJ. Radiological assessment should be used to confirm the diagnosis and its extent. The radiologic assessment of ONJ should incorporate the use of OPG or scintigraphy with MDP as first-line, with dental MRI or spiral dental CT, or CBCT (for bone only) used as more advanced approaches in cases that require further differential diagnosis.

General management of ONJ in patients with osteoporosis (Fig. 1)

A task force was established recently by the American Society for Bone and Mineral Research to address issues related to ONJ after an editorial in the *Journal of Bone and Mineral Research* concluded that "there are insufficient data relating to the risk factors involved to allow construction of evidence-based guidelines for the prevention of ONJ in patients taking oral bisphosphonates for treatment of osteoporosis" [5,58]. Although normal oral health care including visits to the dentist for preventive care should be suggested as part of overall health care, no evidence suggests that any special dental treatment is necessary in osteoporotic patients treated with bisphosphonates. As the only data available on ONJ in patients with osteoporosis are from case reports, treatment of the condition is entirely empirical. As noted, no evidence-based guidelines are available, although numerous professional bodies have issued position statements and recommendations [2,4,5,59,60] and the primary focus of these position statements has been bisphosphonate use in oncology patients.

The treatment of osteoporosis patients who develop ONJ is empirical. There is no data to suggest that stopping bisphosphonate therapy would influence the course of the lesion. Similarly, delaying the onset of bisphosphonate treatment in

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patients undergoing major dental surgery has been suggested. Though this position is not supported by an evidence-based risk/benefit assessment, it fits common sense.

The principle underlying treatment is one of conservative management, with recommendations for patients before treatment with bisphosphonates including: tooth treatment and full epithelial healing before beginning osteoporosis therapy; treating active oral infections and reducing the risk of infections, and routine dental care.

In patients already on bisphosphonate therapy in need of dental intervention, treatment should again be conservative, with concurrent antibiotic coverage. Although there is no scientific evidence for it, some have advocated interrupting bisphosphonate for a few weeks in case of dental surgery, a decision to be taken on a case by case basis. Patients who have developed ONJ during bisphosphonate treatment should be managed in a similar manner to that already described, with conservative treatment where possible. Where indicated, however, necrotic bone should be removed with minimal trauma to adjacent hard and soft tissue, and antibiotic therapy should be administered. Extensive oral surgical procedures should be avoided.

Conclusions

Data relating to ONJ development are currently lacking and diagnosis is based on clinical criteria, with management strategies that are generally conservative. The risk of developing ONJ in osteoporosis patients treated with bisphosphonates is low, with estimates suggesting an incidence of 1 event per 20,000 to 110,000 patient–years. Further complicating the incidence estimate is the fact that the background rate of ONJ in the general population is unknown. Whereas no conclusive data unequivocally link development of ONJ to bisphosphonate intake in osteoporosis, this association should not be understated and appropriate guidance should be provided to patients who express concerns about this issue.

Pathogenesis of ONJ lesions may involve other factors including inflammation and infection, or, less likely, inhibition of angiogenesis. Risk factors for ONJ have not been studied in details but are likely to include trauma to the oral cavity (particularly tooth extraction), use of immunosuppressive drugs, and comorbid conditions. No direct causative relationship has been demonstrated between ONJ and bisphosphonate therapy in patients with osteoporosis. Since the incidence of ONJ in osteoporosis patients appears to be very low, no specific dental management procedures are recommended in this condition.

Conflict of interest

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Consulting fees or paid advisory boards: Servier, Novartis, Amgen, GlaxoSmithKline, Roche, Nycomed, Procter & Gamble.
Lecture fees: Merck Sharp and Dohme, Lilly, Novartis, Servier, Roche, GlaxoSmithKline.
Grants: Novartis, Servier, Procter & Gamble.
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Grants: Procter & Gamble, Eli Lilly, and Amgen.
Erik F. Eriksen
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Grants: Amgen, Chugai, Lilly, Merck, Novartis, Nycomed, Organon, P&G, Pfizer, Roche, Servier, Wyeth.
John T. Grbic
Consulting fees: Novartis, Stock Ownership (less than $10,000) — Merck.
Regina Landesberg
Consulting fees: Novartis, Merck.
Martina Wollenhaupt
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Socrates Papapoulos
Consulting fees: Merck & Co, Novartis, Procter & Gamble, Roche/GSK.
Grants: Merck Sharp & Dohme, Procter & Gamble.
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Consulting fees or paid advisory boards: Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed, NPS, Theramex.
Lecture fees: Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Teijin, Teva, Ebewee Pharma, Zodiac, Analis, Theramex, Nycomed, Novo-Nordisk.
Grants: Bristol Myers Squibb, Merck Sharp & Dohme, Rottapharm, Teva, Lilly, Novartis, Roche, GlaxoSmithKline, Amgen, Servier.
Nansa Burlet, Orhan Sezer, Andrea Laslop, Mats Jontell declared no conflict of interest related to this particular work.

Executive summary

The executive summary of this report is freely available on the web at www.ecceo8.org/images/mail/osteonecrosis_jaw.pdf.

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