

The EUROPEAN SOCIETY
for CLINICAL and
ECONOMIC ASPECTS
of OSTEOPOROSIS
and OSTEOARTHRITIS



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The Impact of Osteonecrosis of the Jaw on
Osteoporosis Management:
Executive Summary of a European Society on
Clinical and Economic Aspects of Osteoporosis
and Foundation for Research on Osteoporosis and
other Bone Diseases Working Group Meeting

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INTRODUCTION

The first reports of osteonecrosis of the jaw (ONJ) in patients taking bisphosphonates to reduce excessive bone resorption were published in 2003. Subsequent reports raised concern and resulted in manufacturers writing letters of caution to physicians and dentists. Recommendations were issued by the US Food and Drug Administration (FDA), and The European Agency for the Evaluation of Medicinal Products (EMA) requested that pharmaceutical companies update their product information and package leaflets.

The European Society on Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Foundation for Research on Osteoporosis and other Bone Diseases Working Group meeting was convened on 14 December 2006 in Geneva to review the available data and published guidelines on this rare but serious condition. The purpose of the meeting was to assess the impact of ONJ on the management of osteoporosis. The discussion focused on the current definition of ONJ, its epidemiology and pathophysiology, as well as identifying potential risk factors. Agreement was also reached on best practice in terms of diagnosis and management.

DEFINITION

Literature reviews suggest that a consensus is emerging with regards to defining ONJ. The following definition was endorsed by the Working Group: *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

For oral bisphosphonates used to treat osteoporosis, the number of spontaneous reports of ONJ submitted to their manufacturers indicates a reporting rate of less than 1 per 100,000 patient treatment years. This occurrence is also corroborated by a German country-wide study. In cancer patients, where IV bisphosphonates are primarily used as adjunct therapy in multiple myeloma and metastatic breast cancer to reduce the number of skeletal related events and treat hypercalcemia, the reported rate is 95 per 100,000 patient treatment years. These figures are based on the spontaneous reporting rates presented by the pharmaceutical company representatives at the meeting, and for alendronate the literature report of 0.7 cases per 100,000 person-years' exposure. Data collected through spontaneous reports should be treated with caution as the reports are not adjudicated, the definition used for diagnosis is not consistent and patient histories are frequently missing critical information. Increased media coverage also resulted in a notable rise in the number of reports.

In risedronate clinical trials in osteoporosis patients, there have been no cases of ONJ reported in approximately 20,000 patients studied for up to 3 years. Clinical data from the HORIZON-PFT study, which evaluated once-yearly zoledronic acid 5 mg in 7,736 women with postmenopausal osteoporosis over 3 years showed no difference in the incidence of ONJ between the treatment and placebo group, with 1 case reported in each group. The reports of ONJ were not spontaneous but were identified by an adjudication committee who actively searched for cases using 50 MedDRA terms.

PATHOGENESIS

The underlying pathophysiological mechanisms behind ONJ have yet to be elucidated. One hypothesis is that bisphosphonates cause an excessive reduction in bone turnover and accumulation of microfractures in the jaw bones, as well as decreasing angiogenesis, leading to bone cell necrosis and apoptosis. The high level of trauma associated with the constant mechanical effects of mastication has led some to believe that the jaws are particularly susceptible to the bone turnover suppression effects of bisphosphonates. However, studies have never demonstrated that bisphosphonates can reduce bone turnover to the extent of adynamic bone. In fact studies in animals and humans have shown that on treatment with bisphosphonates, the skeleton retains the ability to remodel in response to fracture or other stimuli. This suggests that it is unlikely that

low bone turnover is a primary pathogenic contributor to ONJ.

Some researchers have discussed that the antiangiogenic effects of bisphosphonates are involved in the pathophysiology of ONJ. Interestingly, two of the drugs associated with ONJ in oncology patients, cytostatics and steroids, both exert antiangiogenic effects. However, studies in normal bone have shown that zoledronic acid does not inhibit processes that are dependent on angiogenesis, such as new bone formation in remodelling or fracture repair. Conditions associated with cancer, which may promote impaired wound healing and bone infections, may also play a role.

It remains a matter of debate whether ONJ is initiated in the bone and then goes on to affect the mucosa or vice versa. Antibiotics and antimicrobials have been shown to help to some extent in the treatment of ONJ, which suggests microbial involvement. However, the precise role of bacterial infection in this condition is unclear, particularly as pain is often associated with infection but many patients with ONJ present without pain, inflammation, infection, or any other signs or symptoms other than exposed bone.

Until the pathophysiology of this serious condition is fully understood, it is important to note that to date, no conclusive evidence exists that bisphosphonates have a causative link to the development of ONJ in patients with postmenopausal osteoporosis.

RISK FACTORS

Risk factors for the development of ONJ in osteoporosis patients receiving bisphosphonate therapy have not been systematically investigated mainly due to the extremely low incidence. A recent study in cancer patients suggests that higher doses of bisphosphonates, longer treatment duration, dental extractions and periodontitis are all associated with an increased risk of developing ONJ.

The risk of developing ONJ may be increased in patients who, in addition to osteoporosis, have comorbid diseases like rheumatoid arthritis or uncontrolled diabetes. Patients with osteoporosis who are receiving immunosuppressive drugs or are undergoing chemotherapy may also represent an increased risk of developing ONJ.

The following risk factors can be extrapolated for osteoporosis patients receiving bisphosphonates based on case reports and oncology data:

- Invasive oral treatments involving bone exposure. Such treatments may include tooth extraction, subgingival curettage, periapical and periodontal surgery.
- Trauma where bone is exposed to the oral microflora.
- Higher doses of bisphosphonates and longer treatment duration.
- Poor oral hygiene.

There is currently no evidence to suggest that the risk of developing ONJ in osteoporosis patients is increased

if the bisphosphonate therapy is administered intravenously rather than orally.

DIAGNOSIS

Currently, the diagnosis of ONJ is made by the clinical appearance. The key feature of this condition is exposed bone in the mandible, maxilla or both that persists for at least 8 weeks, in the absence of previous radiation to the jaws. Other signs and symptoms may include rough area on the jawbone, 'heavy jaw' or a dull aching sensation, numbness/tingling of the jaw, 'toothache' type pain, soft tissue infection and loosening of teeth. However, as previously mentioned, many patients present with no other signs or symptoms of ONJ other than exposed non-healing bone.

It should be determined if the patient has a history of radiation to the head and neck so that osteoradionecrosis can be ruled out. Osteomyelitis should be treated with appropriate antibiotics and surgical intervention if necessary. In cancer patients metastatic disease should be excluded. It should also be determined if the patient has an underlying systemic condition (such as diabetes or poor nutrition) or is receiving concomitant medications known to impair wound healing.

Biopsies can be used to confirm malignancy, however; histological specimens may be of low quality as physicians are understandably reluctant to remove bone as surgical manipulation

may exacerbate the problem. Hence, biopsy material often is limited to bone sequestra. It is not advisable to take biopsies on a routine basis in patients with no previously known malignancy, i.e. in patients with osteoporosis only. In osteoporosis patients, non-invasive diagnostic procedures, such as a bone scan, radiographic skeletal survey or a CT of the maxillofacial region involved, may be used to exclude malignancy. The relative sensitivity and specificity of different imaging modalities remains to be established. Thus, currently ONJ remains a clinical diagnosis based on inspection of the oral cavity. If ONJ is suspected and there is no evidence of the lesion starting to heal after 8 weeks and it fits the proposed clinical definition of ONJ, the physician should refer the patient to an oral-maxillofacial surgeon immediately.

GENERAL MANAGEMENT

In osteoporosis patients, no specific interventions prior to starting bisphosphonate therapy are required except to encourage routine dental care. If a patient receiving bisphosphonates requires surgery in the maxillofacial region, and risk factors such as diabetes or corticosteroid use are present, close follow-up is recommended and the use of antibiotics and mouth rinses should be considered.

Since the only data available on the treatment of ONJ are case reports, treatment of ONJ is entirely empirical. To date, no treatment has been established to be effective and so the

current approach is conservative management. Some physicians have suggested that a drug holiday from bisphosphonates may be beneficial but there is no evidence to support this.

CONCLUSION

ONJ may not represent a new condition. Literature reviews show, that similar clinical presentations were reported prior to the availability of bisphosphonates, in association with heavy metal, phosphorous and radium exposure; coagulopathies and other cardiovascular factors; and chronic immunosuppressive states. Most frequently mentioned in the context of ONJ is a condition known as 'phossy jaw' or phosphorous necrosis which was reported among matchmakers working directly with white phosphorous in the nineteenth and early twentieth centuries. Since historically potential cases of ONJ have been associated with factors other than bisphosphonates, the background incidence rate of ONJ in the general population remains unknown.

The reporting rate of ONJ with bisphosphonate treatment for non-oncology indications is extremely low at less than 1 per 100,000 patient treatment years. Therefore, it is important to emphasise that although this condition is very serious it does not significantly impact on the risk-benefit ratio for the use of bisphosphonates in osteoporosis for the prevention of fragility fractures, which are themselves associated with much greater morbidity than ONJ and a mortality that ONJ is not known to possess.

It should be noted that due to the scarcity of ONJ data in osteoporosis patients, most recommendations in the literature to date have been based on extrapolations of oncology studies, even when the conclusions drawn are intended for osteoporosis patients. This highlights the need for ONJ registries to be established for osteoporosis patients so that future guidelines are evidence-based.