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Intravenous bisphosphonates in osteoporosis and jaw osteonecrosis: comment on the article by Delmas et al

To the Editor:

We congratulate Delmas and colleagues (1) on their article showing the efficacy of intravenous ibandronate treatment for patients with osteoporosis, as assessed by bone mineral density. New-generation bisphosphonates (NGBs), which initially were used for patients with metastatic bone malignancies, rapidly became used for other bone pathologies such as osteoporosis and Paget’s disease (2,3). Adding to the discussion by Delmas et al, we would like to bring up a potential safety concern about intravenous NGB treatment that has also recently been highlighted by the American College of Rheumatology (4).

During the last 3 years, reports in the otorhinolaryngological literature on avascular jaw osteonecrosis associated with NGB treatment have increased almost exponentially (5,6). NGBs have proved efficacious in oncology patients with bone involvement, and there is no doubt about the contribution of NGBs in improving the quality of life in patients experiencing bone metastases.

In contrast to patients with osteoporosis, oncology patients receive high doses of intravenous NGB and have been shown to be more prone to the development of jaw osteonecrosis. However, jaw osteonecrosis in patients with osteoporosis who are receiving oral NGBs has repeatedly been reported (5,6). Whether these are isolated examples or are cases that suggest a broader clinical problem will become clearer within the next years.

The incidence of jaw osteonecrosis during or after NGB treatment remains unknown, but the rising number of reported cases causes considerable concern. The risk of jaw osteonecrosis seems to depend on the type and dose of NGB administered (5). The fact that osteoporosis patients are usually prescribed oral and lower doses of NGB could explain why these patients are less concerned about jaw osteonecrosis. NGBs inhibit osteoclast activity but also have antiangiogenic effects, and, once incorporated into the bone, they are barely reversible (7).

Considering the higher life expectancy of patients with osteoporosis compared with that of oncology patients, even lower doses of NGB could lead to the delayed occurrence of jaw osteonecrosis (5). Having said this, how early and aggressively NGBs should be prescribed to patients with osteoporosis might be weighed on an individual basis (8). According to the literature (6), the mean time of onset of osteonecrosis after starting intravenous NGB therapy is 1–3 years in oncology patients. Thus, the question of whether intravenous NGB treatment might increase the risk of avascular jaw osteonecrosis seems to depend on the type and dose of NGB administered (5). The fact that osteoporosis patients are usually prescribed oral and lower doses of NGB could explain why these patients are less concerned about jaw osteonecrosis. NGBs inhibit osteoclast activity but also have antiangiogenic effects, and, once incorporated into the bone, they are barely reversable (7).

Therefore, patients with chronic periodontal problems and foreseeable dental extractions should be identified before NGB treatment is started. If necessary, these patients should undergo a specialist dental or maxillofacial workup in order to treat all oral and dental problems before starting NGB ther-
apy. This is particularly important when considering intravenous NGB treatment.

Basile N. Landis, MD
Max Hugentobler, MD, DMD
Hôpitaux Universitaires de Genève
Geneva, Switzerland


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Reply

To the Editor:

We thank Drs. Landis and Hugentobler for their letter highlighting the growing concern among physicians about the case reporting of osteonecrosis of the jaw (ONJ) in patients receiving treatment with bisphosphonates. At present, most reported cases of ONJ have been in oncology patients, with the vast majority of these cases being reported in cancer patients receiving high-dose intravenous (IV) bisphosphonate therapy in association with chemotherapy, radiotherapy, poor dental hygiene, or after a dental procedure. Published series of cases in more than 300 oncology patients have been extensively reviewed (1,2), with additional cases reported in patients with metastatic bone disease or multiple myeloma (3–19). In contrast, few cases of ONJ have been reported in patients receiving bisphosphonates for osteoporosis or osteopenia (1,2,13,18,20–22), and the occurrence of ONJ in this popula-

tion is thought to be very rare. The relationship between bisphosphonate therapy and ONJ in these patients remains unclear, and further investigation is warranted.

The Dosing Intravenous Administration (DIVA) study investigated the effects of ibandronate on bone mineral density and formed the basis of its registration as the first IV bisphosphonate indicated for the treatment of postmenopausal osteoporosis. We have been informed by F. Hoffmann-La Roche Ltd./GlaxoSmithKline that in all controlled clinical trials of patients with postmenopausal osteoporosis receiving ibandronate (IV or oral), no cases of ONJ have been observed, and that the occurrence of this condition will be carefully monitored in future studies and in clinical practice.

As pointed out by Drs. Landis and Hugentobler, patients with chronic periodontal disease and those requiring dental extraction should be identified before bisphosphonate therapy is initiated, although there is no current guideline for their management.

Pierre D. Delmas, MD, PhD
Hôpital Edouard Herriot
Lyon, France

for the DIVA study investigators

13. Migliorati Ca, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of the mandibular and maxillary