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Effect of antiresorptive drugs on bony turnover in the jaw: denosumab compared with bisphosphonates

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Abstract

Osteonecrosis of the jaw as a result of treatment with receptor activators of nuclear factor kappa-B ligand (RANKL) inhibitors (denosumab) is a new type of bony necrosis, the exact pathogenesis of which is unknown. Our aim was to find out whether the turnover of bone in the jaw is increased after denosumab has been given compared with other skeletal sites, and if that turnover might have a role in denosumab-related osteonecrosis of the jaw (DRONJ). Bone scintigraphic images of 45 female patients with breast cancer and bone metastases were analysed retrospectively, and divided into 3 groups: those given denosumab, those given a bisphosphonate, and a control group ($n = 15$ in each). All patients had bone scintigraphy before treatment (T0) and during the course of treatment after 12 (T1) and 24 (T2) months. The data were analysed quantitatively using 6 preset bony regions of interest. There was similar turnover of bone in the mandible compared with other skeletal sites (such as the femur), while the maxilla showed significantly higher turnover. None of the bony regions investigated showed any significant changes after the bisphosphonate had been given. There was a tendency to increase bone turnover in those patients taking denosumab. The bone turnover of the jawbone is not overtly changed either by a bisphosphonate or denosumab, so it seems unlikely that oversuppression of bony turnover in the jawbones plays an important part either in the pathogenesis of DRONJ or in the bisphosphonate-related osteonecrosis of the jaw (BRONJ).

Keywords: RANKL-inhibitor; Xgeva; Denosumab; Osteonecrosis of the jaw; ONJ; Bisphosphonate; BRONJ; Bone turnover; Bone scan; Bone scintigraphy; Pathogenesis

Introduction

Denosumab (a human monoclonal antibody to receptor activator of nuclear factor kappa-B (RANKL)) inhibits the development and activity of osteoclasts, decreases bony resorption, and increases bone density.[1] It is therefore used effectively for the management of osteoporosis

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and metastatic bone diseases.[2] Despite the prophecies in early trial reports,[2] increasing numbers of patients with denosumab-related osteonecrosis of the jaw (DRONJ) have been reported every year since its introduction and approval.[3–6] Because similar prevalences of osteonecrosis of the jaw have been reported in patients taking denosumab and bisphosphonate,[4,7] reaching 5% under denosumab,[8] it is important to recognise the potential problem so that we can introduce preventive measures.

The pathogenesis of ONJ caused by antiresorptive drugs remains to be elucidated and there are different theories, in particular for bisphosphonate-related ONJ. The most popular hypothesis blames the higher bony turnover of the jawbones by antiresorptive drugs that causes oversuppression and results in ONJ.[9,10] However, these finding rely on a few animal studies that are supported by limited data in humans.[11] There are also some inconsistencies in this theory. As osteonecrosis does not manifest itself at other sites, the bony turnover of the jaw consequently has to be higher than that in any other bone in the body. In addition, there has to be a disproportionate inhibition of bony turnover in the jaw compared with the rest of the skeleton after the regular use of denosumab. New approaches are therefore required to investigate whether bony turnover is significantly higher in the jaw than in other bones, and whether there is a change in bony remodelling after RANKL inhibitors or bisphosphonates have been taken.

Nuclear bone scans are the diagnostic method of choice for patients with metastatic bone disease, and are usually available.[12] The uptake of technetium-99m-methylene disphosphonate ($^{99}TC^{m}$-MDP) is associated with both osteoblastic metabolism and blood flow and allows quantitative evaluation of bony turnover.

The goals of this study were to find out firstly whether there is more bony remodelling in the jawbone and, secondly, if the bony turnover of the jaw is considerably altered after denosumab or bisphosphonates have been given compared with other skeletal sites.

Patients and methods

All log books, databases of pictures (PACS, Version R 11.4.1, Philips Medical Systems, Nederland B.V.), and databases of health plans (SAP, Release 6.0, Walldorf, Germany) were used to identify retrospectively all patients with carcinoma of the breast who had routine-staging bone scintigraphy at the Department of Nuclear Medicine between 2011 and 2013 ($n = 630$). We identified all patients with bone metastases ($n = 45$; mean (SD) age 58 (13), range 34–88). They were divided into 3 groups of 15 each: those treated with denosumab, those treated with a bisphosphonate (zoledronate), and a control group that comprised patients with carcinoma of the breast with no bony metastases who were not being given antiresorptive treatment. A further inclusion criterion was that bone scintigraphic images before treatment (T0) were available. Patients in the 2 study groups also had to have had at least 2 follow-up investigations after 12 (T1) and 24 (T2) months of antiresorptive treatment.

All patients in the bisphosphonate group were given zoledronic acid 4 mg intravenously every 4 weeks. All patients in the denosumab group were given denosumab 120 mg subcutaneously every 4 weeks. Patients who had had the maxilla or mandible irradiated, those with metastatic or other bone diseases in the jaw, and those with diffusely increased skeletal tracer uptake were excluded from the study.

Nuclear medicine imaging

For routine staging, follow-up, or control of treatment, the patients were treated by late static whole body bone scintigraphy 2–4 h after intravenous injection of $^{99}Tc^{m}$-MDP 700 MBq using the planar technique. Recordings of the anterior and posterior projections with a table feed of 10 cm/min (>1500 kilo Counts) using a double-headed gamma camera with a high-resolution, low-energy, parallel hole collimator and a large field of view (Symbia T6 or e.cam, Siemens, Germany) in a 256 × 1024 matrix were created with a 10% energy window over the 140-keV photopeak of $^{99}Tc^{m}$-MDP. After the acquisition of the whole-body image, additional shots were taken of the left and right lateral cranium centred in the maxillary and mandibular regions for about 5 min in a 256 × 256 matrix.

Imaging analysis

All imaging analyses were made by the same investigators using OsiriX® Imaging Software (version 5.6, Aycan Digital Systems, Germany) for Mac® OSX 10.7.5 (Apple Inc., Cupertino, CA, US). For the study group all evaluated images were acquired at the same specific investigation points (T): before (T0), and 12 (T1) and 24 months (T2) after deosumab or zolendronate had been taken. Images of the control group were taken during routine staging.

All images were evaluated using the previously described semiquantitative analysis with the OsiriX® ROI.[12] To measure density and signal intensity, 6 regions of interest (ROI) were preselected (Area: 1.001 cm^2, w: 10.0 mm, h: 10.0 mm) and set over right/left lateral views of the cranial scans (0 = background, 1 = posterior maxilla, 2 = anterior maxilla, 3 = anterior mandible, 4 = posterior mandible, 5 = frontobasal) (Fig. 1) and anterior/posterior views of the whole body images (6 = femur) (Fig. 2). The pixel density and the grey value within the ROI correlated with the bone mineralisation and the bony activity. Increased or decreased tracer activity indicated increased or decreased osteoblastic activity. The ROI on the radionuclide