DENOSUMAB-RELATED OSTEONECROSIS OF JAW (ONJ) VERSUS ZOLEDRONIC ACID-RELATED ONJ: DIFFERENT CHARACTERISTICS AT COMPUTED TOMOGRAPHY SCAN EVALUATION? A PROPOSAL FOR A MULTICENTRE STUDY

Riccardo Alberto Campora¹, Vittorio Fusco¹, Stefano Barbero¹, Antonella Fasciolo¹

¹ Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo

Funding: The author(s) received no specific funding for this work.

Potential competing interests: The author(s) declared that no potential competing interests exist.

Abstract

**Background:** Osteonecrosis of the Jaw (ONJ) - related to Bisphosphonates (BPs), denosumab, and other drugs - is a bone disease, that should be evaluated not only on base of clinical features (bone exposure and other signs or symptoms) but also by imaging tools, mostly Computed Tomography (CT) or Cone Beam Computed Tomography (CBCT). An Italian proposal of definition and staging is based on extension of bone alterations at CT scan study. Some scarce literature suggests that ONJ cases observed after denosumab might have different characteristics at CT scan.

**Methods:** We reviewed CT relevant images at ONJ sites of patients developing ONJ after denosumab treatment only, looking for presence of radiological alteration signs. “Early signs” included: cortical disruption; markedly thickened and sclerotic lamina dura; trabecular thickening; focal bone marrow sclerosis; persisting alveolar socket; sequestra formation; widening of periodontal ligament space. “Late signs” included: oro-antral fistula; pathologic fracture; prominence of the inferior alveolar nerve canal; osteolysis extending to the sinus floor; diffuse osteosclerosis;
osteosclerosis of adjacent bones (zygoma; hard palate); periosteal reaction; sinusitis. Cases of patients receiving BPs and shifted to denosumab were excluded. The results were compared with similar data collected by CT scans of ONJ patients treated with zoledronic acid only. The ONJ stage according to Italian staging system (stage 1, focal ONJ; stage 2, diffuse ONJ; stage 3, complicated ONJ) was adopted in both the groups. Results: We evaluated CT scans of patients treated with denosumab, developing ONJ. After exclusion of patients shifted to denosumab after bisphosphonates, 8 patients were found as receiving denosumab only and their CT scan findings were compared with those of 10 ONJ cases observed after zoledronic acid treatment, randomly selected in a database of 103 ONJ cases. The stage resulted more advanced in cases after zoledronic acid treatment. Preliminary analysis indicate that frequency of the single characteristics might be slightly different in the two patient populations; particularly diffuse osteosclerosis was less frequent in this little sample of patients receiving denosumab (2 out of 8 cases) in comparison with those ones receiving zoledronic acid (7 out of 10 cases). Conclusions: A large multicentre retrospective and prospective study is warranted and hopeful, aimed to clarify the differences on CT alterations in denosumab-related and BP-related ONJ cases.

Background: ONJ after treatment with Bisphosphonates (BPs) was firstly recognized on 2003, and it was largely described as BRONJ (BP-related ONJ). Definition and staging of BRONJ are controversial; the AAOMS definition is much restricted, based only on clinical features (bone exposure, lasting more than six weeks), not assuming the importance of bone study with imaging tools. An alternative definition has been published by a committee of members of Italian Societies of Oral Medicine (SIPMO) and Maxillofacial Surgery (SICMF), based on imaging evaluation, essentially Computed Tomography (CT) scan. After 2009, ONJ cases were also observed after treatment with denosumab (an antiresorptive drug different from BPs) and after antiangiogenic drugs (even without association of BPs or denosumab). A recent issue is: do denosumab-related ONJ cases have the same characteristics of BRONJ? Are different both as clinical behavior and at imaging exams? Some scarce literature data are suggesting of somewhat radiological differences, as recently reported. However, the reports are unconsistent, varying from lower bone density values to higher frequency of sequestrum and periosteal reaction, to viceversa less common sequestra and lysis of cortical border for ONJ cases observed after denosumab treatment, in comparison with BP-related cases. We have experience of studies of CT scan evaluation in ONJ cases and we decided to analyse the CT scan findings of recently observed ONJ cases related to denosumab treatment in comparison with some cases related to zoledronic acid, already evaluated and present in our database.

Methods: We reviewed relevant images at ONJ sites of patients developing ONJ after zoledronic acid or denosumab treatment, looking for presence of radiological alteration signs, described by Bedogni et al. and included in ONJ management recommendations by Italian Societies of Oral Medicine (SIPMO) and Maxillofacial Surgery (SICMF). “Early signs” included: cortical disruption; markedly thickened and sclerotic lamina dura; trabecular thickening; focal bone marrow sclerosis; persisting alveolar socket; sequestrum formation; widening of periodontal ligament space. “Late signs” included: oro-antral fistula; pathologic fracture; prominence of the inferior alveolar nerve canal; osteolysis extending to the sinus floor; diffuse osteosclerosis; osteosclerosis of adjacent bones (zygoma; hard palate); periosteal reaction; sinusitis.
Cases of patients receiving BPs and shifted to denosumab were excluded. The results were compared with similar data collected in CT scans of ONJ patients treated with zoledronic acid only, randomly selected among ONJ cases of our hospital database. The ONJ stage according to Italian staging system (stage 1, focal ONJ; stage 2, diffuse ONJ; stage 3, complicated ONJ) was adopted in both the groups[5][6].

Results: We evaluated CT scans of patients treated with denosumab, developing ONJ. After exclusion of patients already treated with BPs and then shifted to denosumab, 8 patients were found as receiving denosumab only: 7F, 1M; 6 breast cancer patients, 2 others; site: 3 with mandible site, 5 maxillary bones; AAOMS stage: 4 stage 0, 1 stage 1; 2 stage 2; SIPMO-SICMF stage: all stage 2 (2 stage 2a, 6 stage 2b). The presence of the early signs was as follows: cortical disruption in 6; markedly thickened and sclerotic lamina dura in 2; trabecular thickening in 7; focal bone marrow sclerosis in 7; persisting alveolar socket in none; sequestrum formation in 1; widening of periodontal ligament space in 4. The “late signs” were as follows: oro-antral fistula in none; pathologic fracture in none; prominence of the inferior alveolar nerve canal in 1; osteolysis extending to the sinus floor in none; diffuse osteosclerosis in 2; osteosclerosis of adjacent bones (zygoma; hard palate) in none; periosteal reaction in none; sinusitis in none (see Table 1).

Table 1. Computed Tomography (CT) signs in denosumab-related and zoledronic acid-related ONJ cases.

| Characteristics                                      | Denosumab-related ONJ (present/total) | Zoledronic acid-related ONJ (present/total) |
|------------------------------------------------------|---------------------------------------|--------------------------------------------|
| Early signs                                          |                                       |                                            |
| cortical disruption                                  | 7/8                                   | 10/10                                      |
| markedly thickened and sclerotic lamina dura         | 2/8                                   | 7/10                                       |
| trabecular thickening                                | 7/8                                   | 10/10                                      |
| focal bone marrow sclerosis                           | 7/8                                   | 0/10                                       |
| persisting alveolar socket                           | 0/8                                   | 0/10                                       |
| sequestra formation                                  | 1/8                                   | 0/10                                       |
| widening of periodontal ligament space               | 4/8                                   | 7/10                                       |
| Late signs                                           |                                       |                                            |
| oro-antral fistula                                    | 0/8                                   | 0/10                                       |
| pathologic fracture                                   | 0/8                                   | 0/10                                       |
| prominence of the inferior alveolar nerve canal       | 1/8 (1/3 mandible)                    | 1/10 (1/6 mandible)                       |
| osteolysis extending to the sinus floor              | 0/8 (0/5 maxilla)                     | 0/10 (0/4 maxilla)                        |
| diffuse osteosclerosis                                | 2/8                                   | 7/10                                       |
| osteosclerosis of adjacent bones (zygoma; hard palate); | 0/8                                   | 0/10                                       |
| periosteal reaction                                   | 0/8                                   | 1/10                                       |
| sinusitis                                            | 0/8 (0/5 maxilla)                     | 2/10 (2/4 maxilla)                        |

The 10 zoledronic acid-related ONJ cases were: 4F, 6M; 4 breast cancer patients, 6 others; site: 6 with mandible site, 4 maxillary bones; AAOMS stage: 3 stage 0, 1 stage 1; 5 stage 2; 1 stage 3. SIPMO-SICMF stage: 2 stage 1 (1 stage 1a and 1 stage 1b), 7 stage 2 (1 stage 2a, 6 stage 2b), 1 stage 3. The presence of the early signs was as follows (see Fig 1): cortical disruption in all 10 cases; markedly thickened and sclerotic lamina dura in 7; trabecular thickening in 10; focal
bone marrow sclerosis in none; persisting alveolar socket in none; sequestrum formation in none; widening of periodontal ligament space in 7. The “late signs” were as follows: oro-antral fistula in none; pathologic fracture in none; prominence of the inferior alveolar nerve canal in 1; osteolysis extending to the sinus floor in none; diffuse osteosclerosis in 7; osteosclerosis of adjacent bones (zygoma; hard palate) in none; periosteal reaction in 1; sinusitis in 2 cases (see Table 1).

Conclusions: Preliminary analysis indicate that frequency of the single characteristics might be slightly different in the two patient populations: particularly diffuse osteosclerosis was less frequent in cases observed after denosumab in comparison with those ones receiving zoledronic acid, as well as for other signs (i.e., markedly thickened and sclerotic lamina dura, and trabecular thickening). However, our case series is limited and not well balanced for stage, disease (breast cancer versus other cancers), sex, and length of drug exposure. A large multicentre retrospective and prospective study is warranted and hopeful, aimed to clarify the differences on CT alterations in denosumab-related and BP-related ONJ cases.

References

1. ^ (2007). American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws. Journal of Oral and Maxillofacial Surgery, vol. 65 (3), 369-376. doi:10.1016/j.joms.2006.11.003.

2. ^ Salvatore L. Ruggiero, Thomas B. Dodson, Leon A. Assael, Regina Landesberg, et al. (2009). American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaw à 2009 Update. doi:10.1111/j.1747-4477.2009.00213.x.

3. ^ Salvatore L. Ruggiero, Thomas B. Dodson, John Fantasia, Reginald Goodday, et al. (2014). American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-Related Osteonecrosis of the Jaw—2014 Update. Journal of Oral and Maxillofacial Surgery, vol. 72 (10), 1938-1956. doi:10.1016/j.joms.2014.04.031.

4. ^ a, b A Bedogni, V Fusco, A Agrillo, G Campisi. (2012). Learning from experience. Proposal of a refined definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ). Oral Diseases, vol. 18 (6), 621-623. doi:10.1111/j.1601-0825.2012.01903.x.

5. ^ a, b, c Bedogni A, Campisi G, Fusco V, Agrillo A.. (2013). Raccomandazioni clinico-terapeutiche sull’osteonecrosi delle ossa mascellari associata a bisfosfonati e sua prevenzione. Cleup.

6. ^ a, b, c Giuseppina Campisi, Alberto Bedogni, Vittorio Fusco. (2020). Raccomandazioni clinico-terapeutiche sull’osteonecrosi delle ossa mascellari (ONJ) farmaco-relata e sua prevenzione. Unipapress.

7. ^ Alberto Bedogni, Stefano Fedele, Giorgio Bedogni, Matteo Scoletta, et al. (2014). Staging of osteonecrosis of the jaw requires computed tomography for accurate definition of the extent of bony disease. British Journal of Oral and Maxillofacial Surgery, vol. 52 (7), 603-608. doi:10.1016/j.bjoms.2014.04.009.

8. ^ Stefano Fedele, Giorgio Bedogni, Matteo Scoletta, Gianfranco Favia, et al. (2015). Up to a quarter of patients with osteonecrosis of the jaw associated with antiresorptive agents remain undiagnosed. British Journal of Oral and
1. Jo-Eun Kim, Sumin Yoo, Soon-Chul Choi. (2020). Several issues regarding the diagnostic imaging of medication-related osteonecrosis of the jaw. Imaging Sci Dent, vol. 50 (4), 273. doi:10.5624/isd.2020.50.4.273.

2. ^Nils Heim, Werner Götz, Franz-Josef Kramer, Anton Faron. (2019). Antiresorptive drug-related changes of the mandibular bone density in medication-related osteonecrosis of the jaw patients. Dentomaxillofacial Radiology, vol. 48 (8), 20190132. doi:10.1259/dmfr.20190132.

3. ^Akira Baba, Tazuko K Goto, Hiroya Ojiri, Mutsumi Takagiwa, et al. (2018). CT Imaging Features of Antiresorptive agent-Related Osteonecrosis of the Jaw/ Medication-Related Osteonecrosis of the Jaws. Dentomaxillofacial Radiology. doi:10.1259/dmfr.20170323.

4. ^Sarina E.C. Pichardo, Frans W. Ten Broek, Marta Fiocco, Natasha M. Appelman-Dijkstra, et al. (2020). A comparison of the cone beam computed tomography findings in medication-related osteonecrosis of the jaws related to denosumab versus bisphosphonates: an observational pilot study. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology, vol. 129 (4), 411-417. doi:10.1016/j.oooo.2019.09.010.

5. ^L. Benzi, I. Gallesio, P. Russo, A. Fasciolo, and V. Fusco. (2014). Computed tomography (CT) diagnosis of unexposed osteonecrosis of jaw (ONJ): different aspects of 13 cases. Ann Stomatol (Roma). 2014 Apr-Jun; 5(2 Suppl): 16. Published online 2014 May 9..

6. ^L. Benzi, I. Gallesio, P. Russo, A. Fasciolo, and V. Fusco. (2014). Mandible fracture and other complications due to osteonecrosis of jaw (ONJ): CT aspects of 4 advanced cases. L. Benzi, I. Gallesio, P. Russo, A. Fasciolo, and V. Fusco. Annals of Oncology, vol. 26, v117. doi:10.1093/annonc/mdv346.15.

7. ^V. Fusco, A. Fasciolo, A. Gambino, M. Cabras, et al. (2019). Inadequacy of current definition and staging system of Medication-Related Osteonecrosis of Jaw (MRONJ) released by AAOMS: A computed tomography study in 151 cancer and myeloma patients. Annals of Oncology, vol. 30, v731. doi:10.1093/annonc/mdz265.040.

8. ^Francesco Erovigni, Alessio Gambino, Marco Cabras, Antonella Fasciolo, et al. (2016). Delayed Diagnosis of Osteonecrosis of the Jaw (ONJ) Associated with Bevacizumab Therapy in Colorectal Cancer Patients: Report of Two Cases. Dentistry Journal, vol. 4 (4), 39. doi:10.3390/dj4040039.

9. ^Antonella Fasciolo, Vittorio Fusco, Iolanda De Martino, Manuela Alessio, et al. (2021). Prevention and screening of Osteonecrosis of Jaw (ONJ): the Alessandria experience of a multidisciplinary team on a 900 patient population. Qeios. doi:10.32388/0QK8E2.