Osteoporos Int (2011) 22:369–370
DOI 10.1007/s00198-010-1177-6

LETTER

# Denosumab-related osteonecrosis of the jaws

**A. Kyrgidis · K. A. Toulis**

Received: 7 January 2010 / Accepted: 12 January 2010 / Published online: 20 March 2010


Dear Editors,

Denosumab is a human monoclonal IgG2 antibody that binds selectively and with high affinity to the receptor activator of nuclear factor-κB ligand(RANK-L) and pharmacologically mimics the effect of osteoprotegerin on RANK-L [1, 2] thereby blocking the binding of RANK-L to the receptor activator of nuclear factor-κB(RANK) [1]. Denosumab rapidly decreases bone turnover markers resulting in a significant increase in bone mineral density and reduction in fracture risk [3].

Osteonecrosis of the jaws (ONJ) was initially erroneously ascribed to being a later chemotherapy effect [2, 4]. ONJ became one of the most discussed adverse events in advanced malignancy [5]. Importantly, ONJ has never been reported to be associated with other pharmaceutical agents, except bisphosphonates [2, 4].

The case of a cancer patient who developed ONJ without previous history of irradiation or bisphosphonate administration has been published [6]. In this patient, ONJ was reported to have healed completely following sequestration, 15 months after drug discontinuation [6]. Despite the fact that this is the only case published to date, additional evidence published in scientific meeting proceedings suggest that the condition of ONJ may not be solely associated to bisphosphonates [7, 8]. Results from two randomized clinical trials (RCTs; NCT00321464 [8], NCT00330759 [7]) of denosumab in cancer patients with bone metastases report that ONJ occurred infrequently [7, 8] (Table 1). Both studies have current or prior intravenous or oral bisphosphonate administration in their exclusion criteria [7, 8], thus bisphosphonates as an etiopathological factor for ONJ in those participants who received denosumab can be ruled out. Since ONJ has not been previously described to be associated with other drugs agents administered to cancer patients [2], it can be suggested that these cases of ONJ are related to denosumab administration.

The role of dosing interval and cumulative dose appears to be important regarding development of denosumab-related ONJ. All denosumab RCTs published to date include a dosing interval longer than 3 months and a cumulative dose of not more than 210 mg per 6 months [3]. None of these studies does report any cases of ONJ. On the contrary, preliminary results of both RCTs studying denosumab for the treatment of bone metastases in cancer patients include a monthly dosing interval and a dose of 120 mg per month [7, 8]. It is evident that denosumab-related ONJ could be a dose-related adverse effect. This latter argument has also been reported to apply to bisphosphonate administration [4, 9]. ONJ has been reported to be a much more common event in those patients receiving bisphosphonates for the treatment and prevention of cancer-related skeletal events (mainly intravenously), rather than in those patients receiving bisphosphonates (mainly orally) for non-malignancy indications [10, 11]. Similar to bisphosphonate-related ONJ pharmacosurveillance and reporting history [4], one could anticipate that broad introduction of denosumab into clinical practice, would allow for the recognition of the denosumab-related ONJ adverse effect in a much wider spectrum of prescription indications, including those for non-malignancy [10].

A. Kyrgidis (✉)
Department of Oral and Maxillofacial Surgery,
School of Dentistry, Aristotle University of Thessaloniki,
3 Papazoli St,
Thessaloniki 546 30, Greece
e-mail: akyrgidi@gmail.com

K. A. Toulis
Department of Endocrinology,
424 Military Hospital,
Thessaloniki, Greece

**Table 1** Osteonecrosis of the jaw (ONJ) adverse effect cases reported from preliminary results of clinical trials comparing head to head denosumab with zoledronate for the treatment of bone metastases in patients with cancer

| Study | | Denosumab | NNH | | Zoledronate | NNH | *p* |
|---|---|---|---|---|---|---|---|
| NCT00321464(8) | 1,026 | 20 (2.0%) | 50 | 1,020 | 14 (1.4%) | 71 | 0.39 |
| NCT00330759(7) | 888 | 10 (1.1%) | 91 | 888 | 11 (1.3%) | 77 | 1.0 |
| Total | 1,914 | 30 (1.5%) | 67 | 1,908 | 25 (1.3%) | 77 | |

*NNH* Number needed to harm; since these are head to head comparison trials, the incidence of osteonecrosis of the jaws in the control population was assumed to be zero. NNH was calculated as inverse attributable risk (1/incidence).

Alpha value is set to $0<0.05$. Alpha values reported from original congress reports [7, 8].

Clinicaltrials.gov NCT00321464; sponsored by Amgen Inc and Daiichi Sankyo Co, Ltd

ClinicalTrials.gov NCT00330759; sponsored by Amgen Inc

ONJ has been reported merely from trials of denosumab in patients with metastatic cancer. Thus, one could argue that it is the presence of metastases in the jaws of those patients that has been reported to be denosumab-related ONJ. Similar arguments have been presented prior to the recognition of bisphosphonate-related ONJ [2, 4] resulting in delayed recognition of ONJ as an adverse effect of bisphosphonates [4]. Based on currently available limited evidence, it could be difficult to reject such arguments; however, the previous paradigm of a relatively uncoordinated safety effort for bisphosphonate-related ONJ reporting [4] dictates that it may be important to early inform clinicians about this possible new adverse effect of denosumab.

It has been hypothesized that the introduction of new anti-resorptive agents to the clinician's quiver could allow for the elimination of ONJ adverse effect [2]. It appears that denosumab cannot be such an anti-resorptive agent; more likely the medical community is probably facing a new agent that can induce ONJ. This association appears to be somewhat dose-related and this is a resemblance with bisphosphonate-related ONJ. Common plausible mechanisms for the etiopathogenesis of both denosumab- and bisphosphonate-related ONJ would encompass defective osteoclast differentiation, function, survival, and "fatigue" [12]. When compared to bisphosphonates, denosumab exhibits the advantage of short clearance time. Thus, more feasible treatment and earlier healing of denosumab-related ONJ when compared to bisphosphonate-related ONJ could be anticipated.

**Conflicts of interest** None.

## References


1. Anastasilakis AD, Toulis KA, Polyzos SA, Terpos E (2009) RANKL inhibition for the management of patients with benign metabolic bone disorders. Expert Opin Investig Drugs 18:1085–1102
2. Kyrgidis A, Triaridis S, Vahtsevanos K, Antoniades K (2009) Osteonecrosis of the jaw and bisphosphonate use in breast cancer patients. Expert Rev Anticancer Ther 9:1125–1134
3. Anastasilakis AD, Toulis KA, Goulis DG, Polyzos SA, Delaroudis S, Giomisi A, Terpos E (2009) Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis. Horm Metab Res 41:721–729
4. Edwards BJ, Gounder M, McKoy JM, Boyd I, Farrugia M, Migliorati C, Marx R, Ruggiero S, Dimopoulos M, Raisch DW, Singhal S, Carson K, Obadina E, Trifilio S, West D, Mehta J, Bennett CL (2008) Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. Lancet Oncol 9:1166–1172
5. Coleman RE (2008) Risks and benefits of bisphosphonates. Br J Cancer 98:1736–1740
6. Taylor KH, Middlefell LS, Mizen KD (2010) Osteonecrosis of the jaws induced by anti-RANK ligand therapy. Br J Oral Maxillofac Surg Oct 15. doi:10.1016/j.bjoms.2009.08.030
7. Henry D, von Moos R, Vadhan-Raj S, Hungria V, Spencer A, Hirsh V, Wang J, Jun S, Yeh H, Dansey R (2009) A double-blind, randomized study of denosumab versus zoledronic acid for the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. European Journal of Cancer Supplements, Vol 7, Issue 3, Joint ECCO 15—34th ESMO Multidisciplinary Congress—Proffered Paper sessions 7(3):12
8. Stopeck A, Body JJ, Fujiwara Y, Lipton A, Steger GG, Viniegra M, Fan M, Braun A, Dansey R, Jun S (2009) Denosumab versus zoledronic acid for the treatment of breast cancer patients with bone metastases: results of a randomized phase 3 study. European Journal of Cancer Supplements, Vol 7, Issue 3, Joint ECCO 15—34th ESMO Multidisciplinary Congress—Presidential session II 7 (3):2–3
9. Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis C, Boukovinas I, Koloutsos G, Teleioudis Z, Kitikidou K, Paraskevopoulos P, Zervas K, Antoniades K (2009) Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol 27:5356–5362
10. Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS (2008) Factors associated with osteonecrosis of the jaw among bisphosphonate users. Am J Med 121(475–483):e473
11. Kyrgidis A, Vahtsevanos K (2009) Osteonecrosis of the jaw in patients receiving oral bisphosphonates. Osteoporos Int. doi:10.1007/s00198-009-01089-5
12. Kyrgidis A, Vahtsevanos K (2009) "Fatigue" having a role in the pathogenesis of osteonecrosis of the jaws. Clin Oral Investig 13:479–480