
Article:
Mahatma, M.M., Jayasuriya, R.L., Hughes, D. et al. (8 more authors) (2021) Denosumab after total hip arthroplasty – Authors' reply. The Lancet Rheumatology, 3 (6). e406-e407. ISSN 2665-9913

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We thank Tiwari and Tiwari for their interest in our article,[1] and for their assessment of the value of our findings for the development of a non-surgical treatment for osteolysis after joint replacement. With respect to their itemised queries, we have the following observations:

1. As arthroplasty surgeons, we are highly sensitive to the issue of periprosthetic infection risk that represents a disastrous patient outcome after joint replacement. However, in the meta-analysis of all clinical trials of denosumab (6omg dose, 33 studies including the FREEDOM trial referred to by the correspondents, 22 253 patients) reported by Diker-Cohen et al,[2] there was no reported difference in relative risk of any infection (denosumab versus placebo RR= 1·03; 95%CI 0·99-1·06) nor infection-related mortality (RR= 0·55; 0·20-1·23) between treatment groups. As such, we find this reassuringly in support of the safety of denosumab for use in the setting of osteolysis.
2. The authors rightly point out that the rate of osteolysis in the presence of a ceramic on polyethylene bearing is lower than that associated with a metal on polyethylene one. However, this observation is redundant for both the design and interpretation of this study, as the presence of osteolysis was the primary inclusion criteria. In respect of the proportions of patients with femoral versus acetabular osteolysis and the various AAOS grades, the key question here is whether the mechanism of osteolysis might vary by anatomic site or lesion size to impact the validity of the observed drug effect. We are not aware of any literature that supports the notion that the underlying biology of osteolysis might vary with either lesion site or volume.
3. In respect of systemic bone quality and osteoporosis, the trial baseline biochemical marker data indicates no systematic difference in bone turnover between treatment groups (which we would expect if there were a bias towards a greater osteoporosis prevalence in one of the study groups) that might undermine the validity of the drug treatment findings.
4. Regarding the coefficient of variation, there are no established reporting standards for histomorphometric measurements in the setting of osteolysis. As such, our reporting adds further to the novelty of the study. Further, in clinical trials we look for between group differences to understand the effect of an intervention. A higher intra-observer coefficient of variation has the effect of decreasing power to detect a positive between-group signal, rather than increasing it. Thus, our finding of significant effects of denosumab on both osteoblast surface and on eroded surface can be considered true findings, despite the noise of the observed coefficients of variation.
5. We apologise if there has been any reader confusion in respect of the role of the CT scans. These were used simply as a secondary confirmation of the AAOS osteolysis grade, not to guide biopsy collection. All biopsies were taken at direct naked eye visualisation of osteolytic lesions at revision surgery.

1. Mahatma MM, Jayasuriya RL, Hughes D, et al. Effect of denosumab on osteolytic lesion activity after total hip arthroplasty: a single-centre, randomised, double-blind, placebo-controlled, proof of concept trial. *Lancet Rheumatol* 2021: E195-W203.
2. Diker-Cohen T, Rosenberg D, Avni T, Shepshelovich D, Tsvetov G, Gafter-Gvili A. Risk for Infections During Treatment With Denosumab for Osteoporosis: A Systematic Review and Meta-analysis. *J Clin Endocrinol Metab* 2020; **105**(5).