

# Denosumab after 8 years

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It is now more than 20 years since the alendronate phase 3 program produced the first trials demonstrating global anti-fracture efficacy for an osteoporosis medication [1, 2]. This brought the osteoporosis field into the era of evidence-based medicine. The euphoria that followed from knowing that the interventions we were prescribing really were preventing fractures soon passed as durations of therapy reached 3 years, the endpoint of most fracture prevention clinical trials. A series of unanswered questions then arose. How long should treatment be continued? Are there long-term side-effects? Do these drugs continue to prevent fractures and, if so, is their continued use necessary for sustained fracture prevention? For alendronate, some of these questions were answered by the FLEX trial, which suggested that dose reduction with long-term use did not reduce efficacy, and that for patients whose femoral neck bone density was no longer in the osteoporotic range, drug discontinuation did not negatively impact on fracture rate [3, 4]. Similar data have now been published from the zoledronate extension studies [5].

In the last decade, osteonecrosis of the jaw (ONJ) and transverse stress fractures of the femoral shaft, referred to as atypical femoral fractures (AFFs), have emerged as significant new safety concerns associated with the long-term use of anti-resorptive drugs. Most information on these problems is from case series or from analyses of medical claims databases.

Some such studies have even suggested that the incidence of atypical femoral fractures attributable to bisphosphonate use might exceed the number of hip fractures prevented by these drugs [6], though other analyses do not support this conclusion [7]. In this context, longer-term data from clinical trials become critically important in assessing the ongoing safety and efficacy of medications for osteoporosis. Longer clinical trials are desirable, though maintaining patients at high risk of fracture on placebo raises ethical and practical issues. The next-best option is to continue long-term follow-up of the cohorts of patients involved in the pivotal clinical trials. While not as robust as a long-term randomized controlled trial because a control group is not continued on placebo, this strategy does provide longitudinal data on a well-characterized cohort, allowing fracture rates and adverse events to be related to duration of therapy. It also allows documentation of chronic effects on bone turnover markers and bone density. The loss of a control group for these measures is not such a problem, since current technology usually generates stable measurements, and the evolution of these parameters in placebo-treated women with osteoporosis is already well documented.

The recent report by Papapoulos et al. in *Osteoporosis International* provides important new information regarding the efficacy and safety of the anti-RANKL monoclonal antibody, denosumab [8]. This drug is a potent anti-resorptive which reduces median bone formation rate to zero after 2–3 years use [9], raising concerns regarding over-suppression of bone turnover. In contrast to the bisphosphonates, it is not bound to bone, so its anti-resorptive effects abate rapidly at the end of the 6-month inter-dose interval, possibly allaying these concerns to some extent. These new data from Papapoulos et al demonstrate stable suppression of pre-dose bone turnover markers between 1 and 8 years

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of denosumab use. However, there is a wide range of values of C-telopeptide, indicating that >50 % of patients have bone resorption rates well within the postmenopausal normal range at the time they are due for re-dosing. This appears to contrast with similar data from alendronate and zoledronate, which seem to produce more consistent suppression of resorption [3, 10]. Also contrasting with bisphosphonates is the continued increase in bone density with long-term use, albeit not at the same rate observed in the first 1–2 years of treatment. This is not confined to the spine, where increases often represent accumulation of degenerative artifact rather than improvement in the actual density of bone, but is also observed in the hip and forearm. With zoledronate, total hip density peaks after 4.5 years of treatment at 5 % above baseline, compared with 8 % for denosumab at 8 years.

Consistent with the density and markers findings, fracture rates remain low out to 8 years. These findings need to be interpreted with caution, since there is a steady attrition of patients from the study, from whom data are not available. It is probably the frailer members of the cohort who will discontinue follow-up, and these are the individuals with the highest fracture risk. Therefore, these data may be biased towards under-estimating the true fracture rate. Also, the confidence intervals around estimates of fracture rate are wide as a result of small numbers of events, so circumspection in interpretation is necessary. With these caveats, the Papapoulos study does suggest long-term maintenance of reduced fracture rates to 8 years with denosumab, and no concrete evidence that sustained suppression of bone turnover results in a generalized increase in skeletal fragility.

Also recently published in *Osteoporosis International* is an analysis of a subset of these data from some of the same investigators [11]. This paper re-presents data in Papapoulos, considering the non-vertebral fracture incidence to 7 years (3 years of denosumab or placebo in the core trial, plus 4 years of the study extension during which all subjects received denosumab). The authors focus particularly on fracture rates in year 4 of active treatment, concluding that there is a further 36 % reduction in non-vertebral fracture rate from year 3 to year 4 of denosumab use. Since bone turnover has been stably suppressed for 3 years, it seems biologically implausible that a step change in fracture rate would occur at this time. It is instructive to note the fluctuation in the year-by-year fracture rates, and to note the confidence intervals around these estimates. Fracture rates in years 6 and 7 are very similar to those in year 2. It is also instructive to consider the vertebral fracture rates, only presented in the Papapoulos paper, which apparently doubled between year 2 and years 4–5 of treatment. This is unlikely to be a real effect, as is the change in non-vertebral fracture numbers in the opposite direction over the same period. Both observations highlight the dangers of post hoc analyses not founded on biologically based hypotheses. If vertebral and non-vertebral fractures are summed, then

in year 2, 2.8 % of participants had a fracture, and in years 4 and 5, 2.9 % fractured, suggesting stable fracture incidence. This is also the finding of the just published study of Gnant, which demonstrated stable anti-fracture efficacy of denosumab over 6 years in women receiving aromatase inhibitor treatment for early stage breast cancer [12].

The safety results at 8 years are particularly important. There were eight patients with ONJ, all diagnosed during the study extension, though three were in the cross-over group. This equates to an incidence of ~4/10,000 patient-years. By comparison, there was one case of ONJ in both the zoledronate and placebo groups in Black et al [13], 1 during 1914 patients-years of observation in the study extensions [10, 14], and no cases in the other phase 3 zoledronate study [15]. These data do not suggest a difference in incidences of this problem with these two medications. There were two AFFs with denosumab, one in each group during the extension, equating to ~1/10,000 patient-years. There were no AFFs in the zoledronate extensions, and a rate of 2.3 subtrochanteric fractures/10,000 patient-years was found in a combined database of zoledronate and alendronate trials, though whether any of these fractures were atypical is not known [16]. Thus, these sparse data do not establish a difference in AFFs among these commonly used therapeutic options.

In conclusion, continuous use of denosumab to 8 years appears to be safe and to maintain reduced fracture rates. The suggestion of a further abrupt reduction in fracture risk after year 3 seems improbable to this author, and not well supported by the totality of the data available. When targeted to individuals with a high enough fracture risk for its use to be cost-effective, denosumab represents an important addition to our means of combating the mounting problem of osteoporotic fractures in our aging population.

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