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COMMENTARY

Importance of reversible remodeling suppression with denosumab

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The original notion leading to the development of bisphosphonates (BPs) for treatment of postmenopausal osteoporosis[1] was that they would reduce bone resorption, and allow bone formation to continue. Of course, it turned out that inhibition of resorption by osteoclasts actually resulted in inhibition of bone remodeling, both resorption and the subsequent formation,[2] as they were tightly coupled. Nevertheless, alendronate, and the other BPs, exhibit strong reduction in fracture risk,[1,3–5] and point to the fact that excessive remodeling is the principal factor in the pathogenesis of osteoporosis and fracture.[6] The anti-fracture benefit seemed to be accomplished by several factors: a small increase in bone mass as a result of filling the remodeling space, a halt in the micro-structural deterioration caused by the excess remodeling and, finally, improvement in bone mechanical quality owing to unknown mechanisms.[7] The pivotal studies of BPs showed that remodeling was reduced to levels found in healthy premenopausal women.[8,9]

However, experience in the past 5–10 years with use of BPs has uncovered a concern regarding long-term suppression of remodeling and the emergence of so called 'atypical femoral fractures (AFF)',[10] as well as osteonecrosis of the jaw (ONJ).[11] While patients not on BPs occasionally present with AFF or ONJ, the concern about a causal relationship with remodeling suppression from BPs arose, because, while quite rare, they seemed to be present more commonly in the context of long-term BP treatment. Further, these patients seemed to have iliac biopsy and bone turnover marker (BTM) evidence of very low, or absent, remodeling.[12,13] The mechanism of the resultant skeletal fragility is assumed to be absent, or inadequate, repair of bone microdamage allowing it to accumulate and result in fractures from little or no trauma.[14]

Nevertheless, the causal relationship between AFF or ONJ on one hand and remodeling suppression by BPs on the other has not been firmly established. The doubt exists because both occur rarely in the absence of BP exposure, the epidemiology studies have not clearly demonstrated that they occur more often than chance in BP-treated fracturing osteoporosis patients[11] and transiliac biopsies in untreated fracturing osteoporosis patients occasionally (~5%) exhibit similarly low or absent remodeling.[10] Although BP treatment ordinarily results in lowering of remodeling rates to those found in healthy, non-fracturing premenopausal women,[6] the latter do not exhibit suppression of remodeling to the extent that tetracycline labeling does not appear in their transiliac biopsies.[12,15] Thus, one hypothesis regarding suppressed remodeling and the occurrence of AFF or ONJ in patients on BPs is that a remodeling defect was present before the beginning of treatment.[16] This follows from the suggestion made by these authors that the association between alendronate and AFF may be driven by patient factors rather than alendronate.

This scenario presents a dilemma for the practicing physician. Both ONJ and AFF are serious adverse events in the lives of patients, and have caused a surprising and alarming reduction in use of BPs in fracturing patients because of fear that these are causally related to BP treatment.[10]

It is noteworthy that they did not come to attention during the pivotal trials of BPs, and they seem to be increased in frequency with continuation of BP treatment beyond the length of these trials, leading to suspicion that long-term suppression of remodeling is required for them to be manifest. Further, the terminal half-life of BP retention may be as much as 10 years.[17] This means that continued exposure to BPs may result in their continued accumulation in the skeleton for as long as treatment continues. Finally, remodeling suppression may linger for as long as 1–2 years after stopping a BP, dependent to some extent on the length of time of treatment before discontinuation.

How does the practitioner confront this dilemma?

1. Start BP therapy as late in life as possible. The problem is that treatment may be needed sooner, that is, in the early years of menopause,[18] resulting in a need for very long-term treatment with BPs. This is worrisome because of unknown safety of long-term accumulation of BPs in the skeleton. Hormone replacement or use of a SERM may be appropriate alternatives in these years.

2. Institute a 'drug holiday'[19,20] after some time on treatment with BPs. However, there are no data indicating when to start or stop the 'drug holiday', or whether it reduces the risk of AFF or ONJ. It is clear that after a highly variable length of time, fracture risk will return to pre-treatment levels.[21,22]

3. Do not use a BP if the pre-treatment BTM levels are below normal. The problem here is that the BTM measurements are not precise enough measures of remodeling to determine when bone remodeling is too low to be safe.

A recent entry into the treatment armamentarium for reduction of fracture risk in patients with osteoporosis manifested by low bone mass (DXA *T*-score < -2.5) and/or low-trauma fractures is denosumab, a human monoclonal antibody that neutralizes RANK ligand, a key mediator in formation of osteoclasts.[23] The treatment is accomplished by subcutaneous injections at 6-month intervals. The result is remodeling suppression seemingly more robust than that exhibited by BPs,[24] and accompanied by anti-fracture efficacy comparable to BPs.[5] However, in the context of fear of AFF and ONJ, because of long-term suppression of remodeling, the recent publication by Brown *et al.*[24] offers some interesting considerations. This study enrolled subsets of patients that had been previously enrolled in two studies in which denosumab[23,25] was continued for 24 months. Both studies compared denosumab with alendronate, and one of them,[23] included a third group that was placebo treated. Both treatment and placebo were discontinued at the end of 24 months, and transiliac bone biopsies were performed 21–29 months later. The results were compared with baseline biopsies performed in the placebo group. The biopsies showed that all the static and dynamic (tetracycline labeling) variables were not significantly different from those seen in the baseline biopsies. This rapid recovery of remodeling after discontinuation of denosumab is concordant with the DXA and BTM findings in the study by Bone *et al.*,[25] where serum BTMs rose above baseline by 3 months (~60% above for CTX) or 6 months (~50% above for P1NP), and declined to baseline by 24 months after discontinuing denosumab. Further, BMD measurements of the spine and hip by DXA began to decline within 6 months and reached baseline by 12 months.

The rapid recovery of remodeling after discontinuation of denosumab is in distinct contrast to the prolonged recovery after discontinuation of BPs. While there remains considerable uncertainty regarding the causal relationship between suppression of remodeling and the development of ONJ and AFF, the difference in time of recovery of remodeling between BPs and denosumab deserves attention. Further, AFF have not been reported during denosumab treatment[26] of osteoporosis although this might be because of the comparatively brief time, as denosumab has been available and the fact that both ONJ and AFF seem to require long-term continuous treatment and attendant remodeling suppression for their expression. Recent reports of ONJ occurring in oncology patients treated with denosumab[27] suggest that remodeling suppression, whether by BPs or denosumab, is causally related to ONJ.

If ONJ and AFF are truly causally related to remodeling suppression, potential advantages in using denosumab for treatment of osteoporosis are that recovery of remodeling is rapid after discontinuation, it does not accumulate in the skeleton, onset of remodeling suppression is rapid after beginning treatment and compliance is enhanced by virtue of the fact that one subcutaneous injection guarantees compliance for a period of 6 months.

Potential disadvantages include: more robust remodeling suppression than with BPs, possibility of unexpected side effects of unknown origin with longer experience in its use, the need for injections instead of oral administration and, finally, lack of data on the length of treatment required for the risk of AFF and ONJ to dictate that remodeling suppression should be discontinued. The latter is an important consideration, because most of the advantage of rapid recovery of remodeling is lost if one must wait until a patient already has already suffered AFF or ONJ to know that it should be discontinued.

Clearly, practicing clinicians need more data to understand how to take advantage of the rapid recovery of remodeling when deciding when to discontinue denosumab treatment.

Conflict of Interest

Robert R Recker, MD, MACP, FACP, is a paid consultant for Merck, Lilly, Pfizer, Procter and Gamble, Amgen, Roche, Glaxo Smith Kline and Novartis, and has received grant/research support from Merck, Lilly, Wyeth, Procter and Gamble, Amgen, Roche, Glaxo Smith Kline, Novartis and Sanofi-Aventis through grants to his institution.

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