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## MEETING REPORT

# Osteoporosis research: ECTS 2012

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Although major breakthroughs in osteoporosis treatment were not presented at this year's meeting, there was important new information and valuable reviews of various areas.

### Denosumab

Data from the end of year 3 of the extension of the FREEDOM Study was presented.[1] A total of 2343 postmenopausal women with osteoporosis have now had 6 years of continuous therapy with 60 mg denosumab every 6 months by subcutaneous injection. During the first 3 years of the core study, vertebral fracture incidence was 7.2% in the placebo group and 2.3% in the denosumab group. After a further 3-year treatment, vertebral fracture incidence was 3.5%. For non-vertebral fractures, the incidence fell from 8% in the placebo group to 6.5% in the denosumab group in years 1–3, falling further to 3.8% in those continuing on denosumab for a further 3 years. This indicates >50% reduction in non-vertebral fractures in comparison with the original placebo rate, though such interpretations need to be made with great care because there has been substantial loss of study subjects since the time of original randomisation, as is the case with all such extension studies. However, what is reassuring, is that there is no indication here of an increase in fracture rates as a result of the long-term suppression of bone turnover produced by denosumab. During the extension, there were four cases of osteonecrosis of the jaw, two in the group treated for 6 years and two in the women crossing over from placebo at year 3.

A further presentation from the core FREEDOM Study evaluated the effects of denosumab on cortical and trabecular bone at the radius using dual-energy X-ray absorptiometry and quantitative computed tomography scans in a subgroup of 441 women studied over the first 3 years of the trial.[2] These analyses demonstrated improvements in bone mineral content and polar moment of inertia of the radius in the denosumab group compared with the placebo group. These positive findings need to be viewed in the context of a hazard ratio of wrist fracture of 0.84 ($P = 0.21$) in the entire trial cohort, raising the question as to whether these surrogate measures are useful indices of fracture risk. In a *post-hoc* analysis of a higher-risk subgroup in the FREEDOM Study, a significant reduction in wrist fractures was found.

### Zoledronate

Richard Eastell presented work from the HORIZON Extension Study, assessing bone density response to zoledronate in those women who had originally been randomised to placebo in the core study. Response in total hip bone density to zoledronate was positively related to serum PINP prior to treatment, and inversely related to bone loss in the years prior to zoledronate initiation. The common factor here is likely to be bone turnover—high turnover off therapy results in rapid bone loss, but also to increased responsiveness to antiresorptive therapy.

Andrew Grey presented further data from a study in which osteopenic women were randomised to a single 5 mg infusion of zoledronate, or to placebo. After 5 years follow-up, spine bone mineral density was 4.1% higher in the zoledronate group, and PINP and CTX were at least 40% lower than placebo. Similar data were found in follow-up of osteopenic men who had received two annual infusions of zoledronate and been followed for a further 5 years. These results suggest that this bisphosphonate could be used very infrequently and still produce clinically significant beneficial effects.

### Odanacatib

Five-year data were presented from the ongoing follow-up of patients in the phase II trial,[3] demonstrating increases in spine bone mineral density of 12% in subjects who had received odanacatib 50 mg per week throughout the study. Similar linear increments in density were seen in the proximal femur. This very sustained pattern of bone gain is unique among antiresorptive therapies and does suggest a potential advantage for odanacatib. Whether this advantage will be apparent in the fracture data from the 3-year phase III trial (expected to report later this year) remains to be seen, because longer periods may be necessary to determine its full anti-fracture potential. High-resolution quantitative computed tomography studies of the distal radius were also presented, demonstrating substantial improvements in cortical and trabecular indices at this site.

### Sclerostin Antibody

Preclinical and early clinical work were presented from Amgen's sclerostin antibody programme. In studies in adolescent monkeys,[4] substantial increases in endocortical mineralising

surfaces (from 14% in control to 88% with antibody) were demonstrated in both cortical and trabecular bone. Activation was demonstrated at previously quiescent surfaces, rather than following on from bone resorption. Studies in osteopenic men and women using a variety of dosing regimens have shown increases in spine density of about 5% at 24 weeks, following treatment periods of 8–10 weeks.[5] These bone-density changes were accompanied by the expected increase in serum PINP, but decreases in the bone-resorption marker CTX of ~50% were observed, implying an unexpected antiresorptive effect, and demonstrating dissociation of formation and resorption indices. Supporting the therapeutic potential of this intervention, it was shown to reduce pelvic fracture rates by two-thirds in a mouse model of osteogenesis imperfecta.[6]

### Teriparatide

Muschitz *et al.*[7] presented a randomised, controlled trial of women treated with teriparatide over 18 months, who were randomised to receive alendronate, raloxifene or no additional therapy, during the second half of the their teriparatide treatment. At the trial's end, bone-density increases were greater in those who had the addition of an antiresorptive therapy. Gluer[8] presented a multicentre trial in steroid osteoporosis in which men were randomised to receive teriparatide or risedronate. Both therapies improved bone density, but the changes were substantially greater with teriparatide, emphasising the value of this anabolic agent in steroid-treated patients in particular.

### Calcium

The previous study of Lappe and a recent reanalysis of the Women's Health Initiative, both suggested that calcium plus vitamin D can decrease cancer risk in postmenopausal women. Whether this is an effect of the calcium, the vitamin D or their combination is unknown. To address this question, Bristow *et al.*[9] meta-analysed the effects of calcium monotherapy on cancer risk in 10 500 individuals involved in randomised, controlled trials. Although marginal effects for individual tumours were observed, the relative risk of any cancer was 0.95 (95% confidence interval 0.76–1.18). This implies that vitamin D may underlie the anticancer effects demonstrated in those earlier studies, rather than calcium.

### Conflict of Interest

Dr Reid has received research grants or speaking/consulting fees from Merck, Amgen, Sanofi, Lilly and Novartis.

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