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MEETING REPORT

Osteoporosis treatment at ASBMR 2012

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Sclerostin Antibodies

The osteoporosis treatment scene is more vibrant at present than it has been for some years, with data presented at this year's ASBMR reflecting a number of novel development programmes. Possibly the greatest excitement is being generated by drugs that are antibodies against sclerostin, with AMG785 currently leading in this area. Mike McClung presented data from the AMG785 phase 2 study.[1] This trial enrolled postmenopausal women with femoral neck T-scores between −2.0 and −3.5, and randomized them to placebo, alendronate, teriparatide or one of five subcutaneous dosing regimens of AMG785. Each of these regimens significantly increased bone mineral density (BMD) at the lumbar spine and proximal femur above placebo levels at 12 months, with the greatest increases seen with 210 mg per month. This dose increased spine BMD by 11.3% and total hip BMD by 4.1%, over a year. These effects were significantly superior to those of alendronate or teriparatide. AMG785 increased serum PINP, as expected, and consistently reduced serum CTX within a week of treatment initiation. Mild injection site reactions occurred in 4% of placebo subjects and 12% of those receiving AMG785, but the safety profile was otherwise unremarkable. Thus, AMG785 appears to have both anabolic and antiresorptive properties, producing larger changes in bone density in one year than any other available therapy. It is currently in phase 3 trials.

Phase 1 data were presented by Eli Lilly for blosozumab, which is also a monoclonal antibody directed against sclerostin.[2] Data were presented for single and multiple intravenous and subcutaneous dosing regimens, which demonstrated increases in lumbar spine BMD of up to 7.7% at 3 months. This is clearly another very potent anabolic agent that shows significant promise.

Odanacatib

A second novel therapeutic class is the cathepsin K inhibitors. The biggest news in this area did not come from the ABSMR, but was in a press release several months earlier, indicating that the pivotal phase 3 trial of odanacatib was being closed out early because an interim analysis had shown it to have reached all its primary and secondary fracture efficacy endpoints. The details of the extent of the reductions in fracture risk with odanacatib are unknown, but there were several presentations from other studies assessing this drug. De Villiers[3] presented a 24-month study of osteoporotic women previously treated with alendronate for more than 3 years, who were randomized to either odanacatib 50 mg/week or placebo. In the placebo group, total hip BMD showed a linear decline, reaching −1.9% at 24 months, whereas BMD was stable at the lumbar spine in those on placebo. In contrast, those taking odanacatib showed increases of 1.7 and 0.8% at the femoral neck and total hip, respectively, at 24 months. There were increases in bone turnover markers in the placebo group (BSAP +40, PINP +60, CTX +80 and NTX +30%) reflecting substantial loss of the antiresorptive effects of alendronate over 24 months. In those randomized to odanacatib, more positive changes in BSAP and PINP were observed, whereas NTX decreased almost 20% below baseline. Surprisingly, serum CTX showed similar changes in the odanacatib group to those seen with placebo. This study demonstrates that patients can transition from a potent bisphosphonate to odanacatib and will have modest further increases in bone density as a result. Bone turnover is generally less suppressed with odanacatib than with alendronate, though the direct effect of odanacatib on the production of the peptides used to assess bone resorption does complicate the interpretation of the bone resorption data.

In a separate study, 214 postmenopausal women with low bone density were randomized to odanacatib 50 mg per week or placebo, and changes in the distal radius and tibia assessed using high resolution quantitative computed tomography and finite element analysis.[4] Odanacatib showed significant beneficial effects on both trabecular and cortical densities, and substantially increased cortical thickness (compared with placebo) at both sites. Whether this will result in greater reductions in non-vertebral fracture rates than are achieved with the bisphosphonates will be known in the coming months when the data from the phase 3 trial are presented. The extent of this reduction will be critical in determining whether odanacatib is a significant therapeutic advance.

Denosumab

Although denosumab is already widely marketed, significant new data regarding its efficacy were presented. The extension

to the original phase 3 trial continues, and data relating to 6 years of continuous denosumab therapy were presented.[5] The gains in bone density from baseline to 6 years were 15.2% at the lumbar spine, 7.5% at the total hip and 6.7% at the femoral neck. Fracture incidence remained low during the extension, with non-vertebral fracture rates reaching 1.3% per annum (compared with almost 3% per annum in the placebo group during the original study). The decreases in both vertebral and non-vertebral fractures were shown to be related to the increases in total hip BMD during the study period.[5] The continued reduction in fracture risk is important to note in the context of the bone histomorphometry data at 5 years, which continue to show absence of tetracycline labels in 30% of subjects, and very low bone formation rates.[6]

Leder *et al.*[7] presented an important new study from a 12-month, open-label trial comparing the effects of teriparatide (20 μg per day) with those of denosumab or the combination of teriparatide and denosumab. The 92 women recruited had not used oral bisphosphonates in the previous 6 months and had not used intravenous bisphosphonates or strontium at any time. Bone densities were measured in the femoral neck, total hip and lumbar spine at 3, 6 and 12 months. The greatest numerical change in BMD from baseline was seen with combination therapy at all time points. At 12 months, combination therapy increased the BMD of the total hip by 4.9%, of the femoral neck by 4.7%, of the lumbar spine by 9.1% and of the one-third radius site by 2.7%. These changes are comparable to those reported with the highest dose of AMG785 in the phase 2 study discussed above. They suggest greater synergism between parathyroid hormone and denosumab than has been documented previously for either alendronate[8] or zoledronate.[9] Much larger studies will be necessary to determine the anti-fracture efficacy of this combined intervention, but based on bone density data, it is the most effective treatment regimen currently available.

Calcium and Vitamin D

Although new drugs are able to be assessed with randomized, controlled trials and produce results which are, therefore, widely accepted, controversy continues to dog two of the most widely used interventions in osteoporosis management—supplements of calcium and vitamin D. Although there is no shortage of randomized trial data for each of these supplements, the therapeutic benefits found in these trials have been small and inconsistent. Pharmaceuticals that produce small and inconsistent effects in trials are usually little used, but in the case of calcium and vitamin D, epidemiologists keep the issues simmering through the performance of observational studies, several of which were presented at this meeting. The logic of presenting such studies when data are already available on tens of thousands of subjects in randomized, controlled trials is unclear, and contradicts the accepted hierarchies of quality of evidence, which place randomized, controlled trials well above observational studies. Observational studies should be primarily hypothesis-generating. In the absence of substantial new randomized, controlled trials of calcium or vitamin D being presented at this meeting, most attendees will have departed with their opinions of the merits of these supplements, little changed.

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Conflict of Interest

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

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