

Osteoporosis therapeutics: recent developments at ASBMR

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Introduction

The American Society for Bone and Mineral Research (ASBMR) held its annual conference in Seattle, WA, 9–12 October 2015. This report covers some highlights of key presentations on osteoporosis therapeutics.

Bone mineral density measurement as a predictor of fracture risk during long-term denosumab treatment

Bone mineral density (BMD) measurement in patients on osteoporosis treatment may be a predictor of fracture risk, and a specific *T* score should be further evaluated as a practical goal for therapy. These were the conclusions made by Dr Serge Ferrari (Geneva University Hospital, Switzerland) and colleagues at a presentation of a study where they investigated the relationship between BMD *T* score and fracture risk during osteoporosis treatment with denosumab [Ferrari *et al.* 2015].

The research team had reported at ASBMR in 2014 that 8 years of denosumab treatment (60 mg subcutaneously [SC] every 6 months) resulted in a substantial number of women with osteoporosis achieving non-osteoporotic BMD *T* scores during follow up, so this study was to see whether there was a reduction in fracture risk even in those who achieved *T* scores above -2.5 standard deviations (SD). There were 3902 women in the original FREEDOM trial who received 3 years of denosumab treatment (60 mg SC every 6 months): a subset of 2343 women was enrolled in this 5-year open-label extension trial to receive long-term denosumab. Total hip BMD and nonvertebral fracture incidence were measured over the entire 8-year period.

The results showed that the incidence of nonvertebral fracture was lower the higher the total hip BMD *T* score [Papapoulos *et al.* 2015]. Interestingly, this inverse relationship between total hip BMD *T* score and nonvertebral fracture incidence was maintained regardless of age or

prior fracture. Dr Ferrari stated that this result argued for continued assessment of BMD during therapy for osteoporosis to predict fracture risk.

Persistently good results with 10 years of denosumab treatment

Henry Bone (Michigan Bone & Mineral Clinic, Detroit, MI, USA) and colleagues reported results for the final year of the 7-year denosumab extension of the FREEDOM study [Bone *et al.* 2015a]. There were 3902 women with postmenopausal osteoporosis who received denosumab (60 mg SC Q6M) for 3 years during the FREEDOM trial and 2343 went on to continue to receive the same dosage for another 7 years. The placebo group in the original trial consisted of 3906 women, and 2207 of these crossed over to receive denosumab (60 mg SC every 6 months) for the next 7 years. At the start of year 10, 2784 of 4550 patients (61%) managed to continue treatment and 80% of them (i.e. 2212 patients) had completed their final 10-year visit (120 discontinued and 452 were still to complete their 10 years).

In those patients who had received a total of 10 years' denosumab therapy, there were significant increases in both lumbar spine and total hip BMD (percentage changes from baseline of 21.7% and 9.2%, respectively). The crossover group had mean cumulative 7-year gains in BMD of 16.5% (lumbar spine) and 7.4% (total hip) from the extension baseline ($p < 0.05$ for both long-term and crossover groups *versus* FREEDOM and extension baselines). Bone turnover markers showed similar and sustained reductions in both group, with attenuation of effect at the end of the dosing period. The yearly rate of new vertebral and nonvertebral fractures remained low. Adverse events and serious adverse events were similar to those previously reported in the extension study.

Thus, denosumab treatment over 10 years leads to a persistent reduction of bone turnover with

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continuing progressive increases in BMD even at the total hip, i.e. with no therapeutic plateau and a continued low fracture incidence. In addition, there were no new safety issues detected and the benefit/risk profile among this group of postmenopausal women remained favourable.

Therapeutic potential of combined denosumab plus teriparatide in patients with severe osteoporosis

The rationale behind sequential or combination therapy in osteoporosis is to provide longer-term benefit to osteoporotic patients compared with single-drug therapy. The DATA trial and its extension showed that up to 2 years of combined teriparatide and denosumab therapy in postmenopausal women increased BMD at the spine, hip, and femoral neck more than either drug alone [Leder *et al.* 2014; Tsai *et al.* 2013]. The same research group has investigated this further, showing that switching from teriparatide to denosumab in postmenopausal osteoporotic women led to continuing improvement in BMD, whereas the opposite switch resulted in progressive reductions in radial BMD and transient BMD decreases at the hip and spine [Leder *et al.* 2014]. The DATA-HRpQCT study looked at the effect of denosumab/teriparatide, combined or each alone, over 12 months on BMD, bone architecture and bone strength, and showed that combination therapy improved bone quality more than either of the monotherapies [Tsai *et al.* 2015b].

Dr Joy Tsai (Massachusetts General Hospital, Boston, MA, USA) and colleagues presented their results from the DATA Switch-HRpQCT study where the effect of denosumab and teriparatide transitions on peripheral BMD and microarchitecture have been assessed [Tsai *et al.* 2015a]. Postmenopausal women with osteoporosis who completed the DATA study were eligible for enrolment, as follows:

- women who received denosumab 60 mg every 6 months for 2 years were switched to teriparatide ($n = 27$) for years 3 and 4;
- women who received either teriparatide 20 mg daily ($n = 27$) or teriparatide plus denosumab ($n = 23$) were switched to denosumab alone.

High-resolution peripheral quantitative computed tomography (HRpQCT) was used to measure total, trabecular and cortical volumetric BMD

(vBMD), cortical thickness and trabecular microarchitecture of the radius and tibia.

The results showed that patients given denosumab after teriparatide had increased cortical vBMD and cortical thickness. However, when teriparatide was given after denosumab there was a decrease in total vBMD, cortical vBMD and cortical thickness, and no change in trabecular vBMD. Patients who were on the combination therapy followed by denosumab showed the greatest cumulative improvements in peripheral cortical microarchitecture ($p < 0.005$ all comparisons).

The researchers concluded that their results provide further credibility to the therapeutic potential of combined denosumab plus teriparatide in patients with severe osteoporosis although switching from denosumab directly to teriparatide might not have beneficial effects on bone structure at least in the short term.

Odanacatib shows consistent fracture risk reduction in subgroups...

Odanacatib is being studied for the treatment of osteoporosis in postmenopausal women in the phase III Long-Term Odanacatib Fracture Trial (LOFT) [Bone *et al.* 2015b]. Study reports suggest it significantly reduces fracture risk, with progressive increases in BMD at the lumbar spine and total hip compared with placebo; however, the cardiovascular risk profile (major cardiovascular events including risk of stroke) is still under adjudication.

Ken Saag (University of Alabama at Birmingham, AL, USA) and colleagues presented a prespecified subgroup analysis of the efficacy of odanacatib in different patient subgroups [Saag *et al.* 2015]. This included 16,713 women (recruited at 387 centres across 40 countries), aged 65 years and older who had no baseline radiographic vertebral fracture and a total hip or femoral neck BMD T score between -2.5 and -4.0 , or with a prior vertebral fracture and a total hip or femoral neck T score between -1.5 and -4.0 . They were randomized to receive odanacatib 50 mg/week or placebo, with calcium and vitamin D₃ supplementation. Primary endpoints included morphometric vertebral fracture, and hip and nonvertebral fracture. Subgroups included baseline age, race, intolerance to bisphosphonates, prior radiographic vertebral fracture, and baseline BMD.

There were 16,071 patients included in the analyses. Odanacatib showed a consistent risk reduction

for the primary fracture endpoints across all subgroups compared with placebo (vertebral fracture 54%, hip fracture 47%, nonvertebral fracture 23%). There were morphometric vertebral fracture relative risk reductions (RRR) among patients with or without a prior vertebral fracture (51% and 60%, respectively), and in age groups 70 and >70 years (57% and 53%, respectively). Across the three primary endpoints (morphometric vertebral fracture, hip and nonvertebral fracture): baseline lumbar spine BMD RRRs were 54%, 47% and 58%, respectively, and RRRs among bisphosphonate-intolerant patients were 52%, 48% and 17%, respectively.

Saag and colleagues concluded that odanacatib showed a consistent reduction in the risk of new and worsening morphometric vertebral, hip and nonvertebral fracture compared with placebo among all the subgroups included in this analysis.

...and increases bone density and bone strength

Dr Bente Langdahl (Aarhus University Hospital, Denmark) and colleagues presented results of a smaller subgroup analysis of patients from the LOFT study [Langdahl *et al.* 2015]. They investigated the effect of odanacatib on trabecular and cortical bone vBMD by quantitative computerized tomography (QCT) and also estimated whole-bone strength using finite element analysis (FEA). In this study, there were 164 women (recruited at 10 centres in South Africa and Denmark), aged 65 years and older who had no baseline radiographic vertebral fracture and a total hip or femoral neck BMD *T* score between -2.5 and -4.0 , or with a prior vertebral fracture and a total hip or femoral neck *T* score between -1.5 and -4.0 . They were randomized to receive odanacatib 50 mg/week (78 patients) or placebo (86 patients), with calcium and vitamin D₃ supplementation. The primary endpoint was the per cent change from baseline in trabecular vBMD at the spine after 24 months of treatment, and a secondary endpoint was cortical vBMD at the total hip. Also, QCT endpoints comprised other trabecular, cortical and integral parameters at the spine and hip and estimated whole-bone strength using FEA.

After 24 months, odanacatib was shown to increase spine (L1) and total hip trabecular, cortical and integral vBMD compared with baseline ($p < 0.001$ in all cases), whereas placebo did not.

Whole-bone estimated strength at the L1 vertebra and proximal femur was increased among patients

who received odanacatib, but it remained the same or decreased in patients assigned to placebo. In summary, this subgroup placebo-controlled study in postmenopausal women with osteoporosis showed that odanacatib increased trabecular, cortical and integral vBMD in the spine and total hip, and increased the estimated (FEA) strength at the vertebrae and total hip.

Abaloparatide decreases the incidence major osteoporotic fractures in postmenopausal women...

Abaloparatide is an analogue of parathyroid hormone-related protein, a hormone that regulates bone development. The phase III Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) trial comprises 2463 postmenopausal women of whom almost half had suffered a previous nonvertebral fracture, and a third had experienced one or more vertebral fractures. They were given subcutaneous abaloparatide (80 µg daily), placebo or teriparatide (20 µg), plus calcium and vitamin D for all patients, over 18 months.

Results were reported at the Endocrine Society conference in March 2015 [Miller *et al.* 2015]. They showed that abaloparatide reduced the rate of new vertebral fractures to only 0.58%, compared with a 4.2% rate seen among placebo patients (a reduction of 86%; $p < 0.0001$). The rate was reduced to 0.84% in the teriparatide group (an 80% reduction compared with placebo; $p < 0.0001$). For nonvertebral fractures, abaloparatide produced a 43% reduction compared with placebo (2.7% versus 4.7%, respectively; $p = 0.0489$), and a 45% reduction in clinical fractures was seen (3.9% versus 8.3% with placebo; $p = 0.0112$). There was no significant difference in the rate of nonvertebral and clinical fractures in the teriparatide and placebo groups ($p = 0.2157$ and 0.1127 , respectively).

Dr Lorraine Fitzpatrick (Radius Health, Waltham, MA, USA) and colleagues reported the incidence of major osteoporotic fractures (i.e. high or low trauma clinical fractures of the upper arm, forearm, hip, shoulder, and/or spine) [Fitzpatrick *et al.* 2015]. Abaloparatide significantly reduced major osteoporotic fracture compared with placebo by 67%: fracture rates of 1.2% and 3.8%, respectively; $p = 0.0014$. The fracture rate with teriparatide (2.7%) was not significantly different from placebo ($p = 0.2028$). There was a significant difference between abaloparatide and teriparatide fracture rates ($p = 0.0437$).

The authors concluded that abaloparatide over 18 months significantly decreased the incidence of major osteoporotic fractures compared with placebo and teriparatide.

...and follow-on alendronate appears to continue fracture reduction among abaloparatide patients

Dr Felicia Cosman (Helen Hayes Hospital, West Haverstraw, NY, USA) and colleagues described the ACTIVEExtend trial where 1139 eligible subjects who had received abaloparatide or placebo for 18 months in the ACTIVE trial are now getting alendronate (70 mg per week) for an additional 24 months [Cosman *et al.* 2015]. Assessment includes clinical fracture assessment, BMD, bone marker, and safety evaluations every 6 months, and vertebral fracture assessments at 6 and 24 months. Preliminary results were presented for risk reduction of vertebral and nonvertebral fractures at 6 months. They showed that 1.23% (i.e. 7 of 568 patients) in the placebo/alendronate group had new vertebral fractures in the extension period compared with 0% (i.e. 0 of 544) abaloparatide/alendronate recipients. Similarly for nonvertebral fractures, the rates were 1.2% (i.e. 7 of 581 patients) in the placebo/alendronate group and 0.5% (i.e. 3 of 558) abaloparatide/alendronate recipients.

Romozumab improves strength at the lumbar spine and hip

The monoclonal antibody romozumab is a bone-forming agent that inhibits sclerostin (an osteocyte-derived inhibitor of osteoblast activity). In 2014, McClung and colleagues published the results of a phase II, placebo-controlled study with romozumab in 419 postmenopausal women with low bone mass [McClung *et al.* 2014]. They showed that romozumab (70–210 mg SC monthly or 140–210 mg every 3 months over 12 months) increased BMD and bone formation, and decreased bone resorption. The effect was greater with romozumab compared with placebo and also two active drug comparators (alendronate and teriparatide). A subset of these women were selected for spine and hip QCT imaging, which confirmed the BMD gains at the spine and hip for romozumab versus teriparatide on integral vBMD.

Dr TM Keaveny (University of California, CA, USA) and colleagues described the results of FEA

on the QCT scans at the lumbar spine and total hip of patients who had received subcutaneous romozumab 210 mg monthly, placebo, or teriparatide (20 µg daily) for 12 months [Keaveny *et al.* 2015].

The estimated strength at the lumbar spine increased by 27.3% from baseline with romozumab, 18.5% with teriparatide, but decreased by 3.9% with placebo (24, 28 and 27 patients, respectively). The estimated strength at the hip increased by 3.6% from baseline with romozumab, but there was no changes for teriparatide or placebo (18, 19 and 9 patients, respectively). The authors concluded that the strength improvements seen with romozumab support its further development and the ongoing phase III clinical program.

Conclusions

The selected abstracts from the ASBMR 2015 demonstrate that further therapeutic advances are continuing in the management of osteoporosis. The long-term follow studies with denosumab give comfort that treatment up to 10 years will show continued benefits in terms of bone mass and structural changes with, in all likelihood, maintained antifracture efficacy. Studies presented examining the potential for the antiresorptive agents, odanacatib and abaloparatide, suggest that these new treatments may well have a role in the clinic very soon when approved by licensing authorities in the USA and Europe. There may well be new anabolic therapies to follow into clinic, with the most advanced of these in terms of clinical investigation being the antisclerostin antibody, romozumab, early data from which is showing very encouraging results.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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