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MEETING REPORT

Osteoporosis treatment (ECTS 2013)

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Meeting Report from the European Calcified Tissue Society Annual Congress, Lisbon, Portugal, 18–21 May 2013

For individuals working in the area of osteoporosis treatment, the European Calcified Tissue Society (ECTS) meeting this year was overshadowed by the death, during the meeting, of Steven Boonen, who has contributed extensively to this area of knowledge and development. As with previous ECTS meetings, Steven was a substantial contributor up until the moment of his collapse, which makes his sudden loss all the more poignant. He will be greatly missed by his colleagues around the world. With respect to research presentations, there were no major breakthroughs announced, but there is the continuing emergence of positive and exciting data regarding bone anabolic therapies, and continuing additions to our knowledge of other established therapies.

Anabolics

Eli Lilly led the way with the presentation of their Phase 2 study of blosozumab, an antibody directed against sclerostin.[1] The study enroled 154 postmenopausal women with lumbar spine *T*-scores between −2.0 and −3.5, and randomised them to receive placebo or blosozumab at doses of 180 mg every 2 weeks, 180 mg per month or 270 mg every 2 weeks over a year. In a study addendum, additional participants were randomised to blosozumab at a dose of 270 mg every 12 weeks or to placebo. There were dose-related increases in lumbar spine bone mineral density (BMD) with each of the blosozumab regimens, and all were significantly superior to placebo. The spine BMD increase at 12 months was 6.7% with a dose of 270 mg every 3 months, 8.4% with 180 mg per month, 13.9% with 180 mg per fortnight and 17.8% with 270 mg per fortnight. These are among the largest bone density responses documented with any treatment for osteoporosis, and reinforce the promise of the anti-sclerostin antibodies. Apart from mild-to-moderate injection-site reactions, the adverse event profiles were similar for placebo and blosozumab.

These findings were complemented by work presented by Claus Glüer's group, describing the effects of the Amgen anti-sclerostin antibody romosozumab.[2] Quantitative computed tomography (QCT) and high-resolution QCT were carried out in subgroups of men and women involved in a small Phase 1B study that administered a range of drug doses for 3 months, and then followed up responses over a subsequent period of 3 months without further treatment. The pooled romosozumab groups showed improvement at 3 and 6 months in a variety of trabecular and cortical indices, including a 34% increase in stiffness at 6 months. These results suggest that these antibodies have efficacy in both cortical and trabecular bone compartments in the spine.

Hattersley *et al.*[3] introduced a novel analogue of hPTHrP (1–34), which has been developed by Radius, a Boston biotechnology company. Two-hundred and twenty-one postmenopausal women with osteoporosis were randomised to receive daily subcutaneous injections of 20, 40 or 80 μg of BAO58 over 24 weeks. These treatments were compared with placebo or teriparatide at doses of 20 μg per day. In the spine, the 80-μg dose of BAO58 increased BMD by 6.7%, in comparison with 5.5% for teriparatide. At the total hip, this dose of BAO58 increased the density by 2.6% compared with 0.5% for teriparatide. In the subset of patients continuing treatment up to a year, the spine BMD increase was 12.9% with BAO58 and 8.6% with teriparatide, compared with hip BMD increases of 2.7 and 1.2%, respectively. Thus, this novel PTHrP analogue was marginally superior to teriparatide in the spine, but does appear to have better short-term efficacy at the hip. Radius has now completed enrolment of 2400 subjects into a Phase 3 fracture trial of this drug.

Antiresorptives

The bisphosphonates remain the most widely used agents for the management of osteoporosis, and there continues to be a focus on their non-bone effects. As mortality was demonstrated to be diminished with zoledronate and in a meta-analysis of all effective osteoporosis therapies, there has been interest in the cardiovascular effects of bisphosphonates. Grove *et al.*[4] reported a nationwide retrospective cohort study from Denmark, in which all users of bisphosphonates were compared with control groups for the occurrence of heart failure. There appeared to be a 31% increase in the risk of heart failure associated with bisphosphonate use, which contrasted with a nonsignificant relative risk of heart failure in raloxifene users of 1.07. However, when the risk of heart failure was studied across refill compliance strata, it was found that the risk increased with increasing refill compliance for etidronate, whereas it decreased for alendronate ($P<0.01$ for both). These data could

be interpreted in a variety of ways, but provide some support for the suggestion of cardio-protection from potent bisphosphonates, although why this particular cardiac end point was chosen rather than more conventional cardiovascular events such as myocardial infarction or stroke is unclear.

There continues to be concern about the occurrence of atypical subtrochanteric femoral fractures in long-term users of bisphosphonates, and thus the report from Morin *et al.*[5] that the geometry of the femur is a significant risk factor for the development of these fractures was of interest. A femur shape that results in greater load on the lateral femur may make subjects more susceptible to the risk of these fractures. This is of great interest in terms of understanding the pathogenesis of this problem, but whether these assessments will prove to be clinically useful in predicting who is at risk of this fracture type is not yet clear.

Fracture risk calculators are now in routine clinical use, often in subjects who are already taking therapies for osteoporosis. However, the available calculators have all been developed in treatment-naive populations, and thus the study from Cummings *et al.*,[6] determining predictors of fracture risk during denosumab treatment, is important. They found that vertebral fracture risk was determined by body mass index (BMI), and baseline spine and hip BMDs, was further influenced by percent change in total hip BMD during treatment and by incident fractures. For non-vertebral fractures, BMI, baseline hip BMD and serum C-telopeptide, together with incident fracture, were predictive. Thus, baseline risk factors remain important predictors of fracture risk during treatment, but incident fractures and total hip bone density response on treatment are also important contributors.

Other Current Therapies

In recent years, there has been active promotion of devices that produce whole-body vibration as a way of improving bone health. Some animal data have suggested that this intervention is efficacious. Kiel *et al.*[7] reported a randomised, controlled trial that compared 10 min of daily whole-body vibration with a sham treatment in 174 older men and women who were not taking bone-active drugs, other than calcium and vitamin D. Spine and hip BMD, assessed by quantitative computed tomography, showed no differences between groups. Biochemical markers of bone turnover were also unaffected by the intervention. Taken together with a previous meta-analysis, which was also negative, these findings suggest that whole-body vibration should not be in clinical use at present.

Testosterone supplementation in older men with osteoporosis, particularly those treated with glucocorticoids (which specifically decrease serum testosterone levels), has been in use for many years, with some clinical trial support. Wagner *et al.*[8] presented a 5-year, randomised, controlled trial in 52 cardiac transplant patients. These men were treated every three months with infusions of ibandronate and were additionally randomised to receive testosterone supplementation. At 5 years, hypogonadal patients randomised to testosterone showed larger increases in femoral neck BMD than did eugonadal patients or hypogonadal patients not given testosterone replacement (12.4% compared with 16.4%). Fracture incidence was reduced in men randomised to testosterone compared with those treated with ibandronate only. Because the numbers of subjects in this study are small, as in previous testosterone studies, these cannot be regarded as definitive findings, but they do build on the existing data to suggest that targeting testosterone replacement to men with demonstrable deficiency is beneficial to bone health. This may have additional benefits in terms of energy levels and libido, but there is ongoing concern regarding prostate cancer risk.

Vitamin D continues to be an area of significant clinical controversy. Data were presented from the AGES-Reykjavik Study, which is a prospective study of almost 6000 elderly subjects from Reykjavik.[9] The present report addressed the relationship between baseline serum 25-hydroxyvitamin D and subsequent risk of hip fracture, after adjustment for a large number of other variables, including measures of frailty. Serum 25-hydroxyvitamin D levels $<30\,\text{nmol}\,\text{l}^{-1}$ doubled the hip fracture risk, but vitamin D levels above $30\,\text{nmol}\,\text{l}^{-1}$ were not related to fracture risk. Reid *et al.*[10] presented rather different data, which led to a generally similar conclusion. In a systematic review of trials of vitamin D supplementation in adults (23 studies in all, including more than 4000 individuals), they found that most studies observed no beneficial effects of supplementation on BMD. When the data are meta-analysed, the only site to show a statistically significant effect was the femoral neck, with an average increase of 0.8% over 2 years. In the spine, total hip, forearm and total body, there was no evidence of beneficial BMD effects. There was a trend for studies in which the mean baseline 25-hydroxyvitamin D level was $<50\,\text{nmol}\,\text{l}^{-1}$ to show a beneficial effect, and vitamin D supplement doses <800 U per day were more likely to be beneficial than higher doses. These findings suggest that the use of vitamin D supplements in adult populations that do not have specific risk factors for vitamin D deficiency is unlikely to contribute to osteoporosis prevention. The Reid study is consistent with the conclusions from the Reykjavik study that maintenance of serum 25-hydroxyvitamin D levels >30–$40\,\text{nmol}\,\text{l}^{-1}$ is probably all that is necessary for the maintenance of adult skeletal health. These findings align with the recommendations of the Institute of Medicine.

Conflict of Interest

Dr I Reid has received research funding and/or consultancy fees from Merck, Sanofi, Amgen and Novartis.

Acknowledgements

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