Denosumab Reduces Bone Turnover, Risk of Fractures for Up to 9 Years in Women With Osteoporosis

Abril 1, 2015

[Presentation title: Denosumab Treatment of Postmenopausal Women With Osteoporosis for up to 9 Years: Results Through Year 6 of the FREEDOM Extension. Abstract OC4]

By Chris Berrie

MILAN, Italy -- April 1, 2015 -- Long-term treatment with denosumab -- for up to 9 years -- provides persistent reduction in bone turnover and continued low incidence of non-vertebral and major non-vertebral fractures for postmenopausal women with osteoporosis, researchers reported here at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO).

The open-label, long-term extension phase from the randomised, placebo-controlled phase 3 FREEDOM trial was presented here on March 27 by Socrates Papapoulos, MD, Leiden University Medical Centre, Leiden, the Netherlands.

In the FREEDOM trial, denosumab 60 mg every 6 months significantly reduced new vertebral (68%), non-vertebral (20%), and hip (40%) fractures in postmenopausal women with osteoporosis. Denosumab also significantly increased bone mineral density (BMD).

The current report presented the data for up to 9 years of denosumab treatment. This included patients who received denosumab in the original study (n = 2343; 9 years of treatment) and patients who received placebo in the original trial, but crossed over to denosumab for the extension trial (n = 2,207; 6 years of treatment).

Changes in the bone turnover markers CTX and P1NP remained stable.

“In other words, there is no sign that perhaps with prolongation of treatment there is a loss of the efficacy of denosumab,” said Dr. Papapoulos.

For the effects of denosumab on non-vertebral fractures in the long-term group, yearly incidence from the extension baseline of 3 years of denosumab (2.2%) was maintained and improved further through 6 years (1.8%) to 9 years (1.1%).

For the cross-over group, the extension baseline for yearly incidence of non-vertebral fractures (2.5%) remained unchanged with the first 3 years of denosumab (2.6%), before showing improvement to 6 years (1.5%).

For hip fractures, the long-term denosumab group showed improvements from the extension baseline (3 years) to 6 years to 9 years with denosumab (0.3% to 0.2% to <0.1%, respectively), as also seen for the cross-over denosumab group (0.3% to 0.2% to 0.1%, respectively).
Rates of serious infections and malignancies were low through 1 to 9 years of denosumab treatment (1.1-2.8 per 100 patient-years).

“The benefit/ risk profile of denosumab remains favourable,” said Dr. Papapoulos.

Funding for this study was provided by Amgen Inc.

Alendronate, Teriparatide Increase BMD in Patients With Glucocorticoid-Induced Osteoporosis

Abril 1, 2015

[Presentation title: Trabecular Bone Score in Patients With Chronic Glucocorticoid Osteoporosis Treated With Alendronate or Teriparatide. Abstract P133]

By Chris Berrie

MILAN, Italy -- April 1, 2015 -- Both alendronate and teriparatide promote significant increases in lumbar spine bone mineral density (BMD) in patients with chronic glucocorticoid-induced osteoporosis, researchers reported here on March 29 at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO).

However, only teriparatide, and not alendronate, significantly increased trabecular bone score.

The trabecular bone score is a new grey-level texture measurement derived from 2D lumbar spine dual-energy x-ray absorptiometry (DXA) images. It is known to correlate with the 3D characteristics of bone microarchitecture, to provide fracture risk predictions independent of BMD and clinical risk factors.

“Our objective were to determine the effects of alendronate and teriparatide on trabecular bone score in this particular patient population,” said Kenneth G. Saag, MD, Division of Rheumatology, University of Alabama at Birmingham, Birmingham, Alabama.

To achieve this, the researchers retrieved the relevant DXA data from a 36-month primary study that compared the benefits of alendronate and teriparatide in patients with chronic glucocorticoid-induced osteoporosis.

This primary study randomised patients to oral alendronate 10 mg/day (n = 214) or injectable teriparatide 20 mcg/day (n = 214), with all patients also receiving the respective placebo plus calcium 1,000 mg/day and vitamin D 800 IU/day.

Of the 118 alendronate completers and 123 teriparatide completers, DXA data of adequate resolution for defining trabecular bone scores were available for 53 and 56 patients, respectively.
“This was done on the DXA machines that had access to this software capacity,” added Dr Saag.

In the primary study over 36 months treatment, both agents provided significant beneficial changes over baseline lumbar spine BMD, and compared with alendronate, there was significant added benefit for teriparatide (P< .001).

Despite the reduced numbers here, this analysis paralleled the primary study, with both alendronate and teriparatide providing significant lumbar spine BMD benefits over baseline (5.5%, 10.3%; P< .05), and with teriparatide significantly better than alendronate (P< .05).

However, for trabecular bone scores, alendronate showed no improvement throughout 36 months of treatment, while teriparatide saw a significant increase compared both to baseline (3.7%; P< .05) and over alendronate (P< .05).

On the basis that the pathogenesis of chronic glucocorticoid-induced osteoporosis is predominantly reduced bone formation, “trabecular bone score could represent a sensitive way to discriminate the treatment effects of an anabolic from the antiresorptive therapy in glucocorticoid-induced osteoporosis, similar to what we see in postmenopausal osteoporosis,” said Dr. Saag.

Funding for this study was provided by Eli Lilly and Company.

WCO is sponsored by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

**Strontium Ranelate Improves Lumbar BMD in Women With Thalassaemia-Related Osteoporosis**

Abril 1, 2015

[Presentation title: Bone Mass and Bone Turn-Over in Women with Thalassemia Major Related Osteoporosis: Effects of Strontium Ranelate. Abstract P487]

By Chris Berrie

MILAN, Italy -- April 1, 2015 -- Strontium ranelate provides significant improvements in lumbar bone mineral density (BMD) and bone turnover markers over 2 years compared with placebo in women with thalassaemia-related osteoporosis researchers said here on March 28 at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO).

For older patients with thalassaemia major, there is considerable morbidity from bone disease due to osteoporosis, often resulting in disabling pain and fractures, according to Antonino Catalano, MD, Centre for Prevention, University of Messina, Messina, Italy.
The researchers evaluated the effects of strontium ranelate on BMD and bone metabolism regulators in 24 women with thalassaemia-major-related osteoporosis. Patients were randomised to placebo (n = 12) or strontium ranelate 2 g/day (n = 12) for 2 years.

There were no significant differences in clinical characteristics between groups at baseline. Another 20 healthy, age-matched women were observed as no-treatment control subjects.

All active-study patients had been maintained on a regular transfusion programme and received oral deferiprone 75 mg/kg/day as an iron chelation treatment; they were also provided with calcium 1 g/day and vitamin D 800 IU/day.

At 24 months, women treated with strontium ranelate increased their spine BMD values in comparison with baseline (+4%; P< .05), but no significant change was observed at femoral neck.

Only in the strontium ranelate group did bone turnover markers significantly change, with a reduction of CTX (0.69 ± 0.19 vs 0.60 ± 0.15 ng/ml at baseline and after 24 months, respectively; P< .05) and an increase of BSAP levels (14.85 ± 1.91 vs 17.3 ± 3.06 U/L; P < .05); sclerostin, but not DKK-1 levels were also reduced by strontium ranelate treatment (-17 %; P< .05).

A significant reduction of back pain was already observed at 18 months (-30 % vs baseline values) in the strontium ranelate group and was maintained at 24months (-60% and -30% vs baseline and placebo values, respectively; P< .05).

WCO is sponsored by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

**Antenatal Supplementation With Cholecalciferol Reduces Prevalence of Vitamin D Insufficiency**

Abril 1, 2015


By Chris Berrie

MILAN, Italy -- April 1, 2015 -- Antenatal supplementation with cholecalciferol 1000 IU/day reduces the prevalence of vitamin D insufficiency, and prevents the gestational reduction in 25-hydroxyvitamin D (25[OH]D) in women who deliver in winter or spring, researchers said here at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO).
Cyrus Cooper, MD, Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom, presented these data on behalf of the MAVIDOS Study Group, here on March 27.

The researchers evaluated maternal antenatal vitamin D supplementation and offspring bone mass measured at birth in pregnant women aged 18 years and older. The women were randomised to placebo (n = 486) or to cholecalciferol 1,000 IU/day (n = 479) and had 25(OH)D levels estimated at 14 weeks gestation and again at 34 weeks gestation. Baseline 25(OH)D levels were 25 to 100 nmol/L.

Both groups has similar 25(OH)D levels at baseline and at 14 weeks gestation. However, by 34 weeks gestation, levels significantly improved for mothers receiving vitamin D supplementation (83.4% vs 36.5%; P < .001).

Across the full analysis population, the offspring bone area and total bone mineral content (BMC) were not significantly affected by vitamin D supplementation.

In considering pre-specified modifiers for treatment interactions between maternal vitamin D supplementation and offspring whole body BMC, no significance was seen for sex of offspring, offspring age at analysis, maternal body mass index, and 14-week 25(OH)D levels.

However, there was unexpected treatment interaction significance for offspring birth season (P = .03). Therefore, the researchers divided the data according to offspring birth season, where a significant increase in offspring whole body BMC was seen for maternal vitamin D supplementation only for winter births (P = .004).

“There is a question is whether these findings suggest a stratified approach to vitamin D supplementation during pregnancy, or whether indeed one can move forward with a population-wide strategy,” noted Dr. Cooper.

WCO is sponsored by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

**Two Years of Romosozumab Followed by Denosumab Improves BMD in Postmenopausal Women**

Abril 1, 2015

[Presentation title: Results of 2 Years of Romosozumab Treatment Followed by 1 Year of Denosumab or Placebo in Postmenopausal Women With Low Bone Mineral Density. Abstract OC3]

By Chris Berrie

MILAN, Italy -- April 1, 2015 -- Romosozumab is well tolerated and increases bone mineral density (BMD) over 2 years, compared with placebo, in postmenopausal women with low
BMD, researchers reported here on March 27 at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO).

Furthermore, these benefits were significantly increased when denosumab was taken after romosozumab treatment.

Michael R. McClung, MD, Oregon Osteoporosis Center, Portland, Oregon, and colleagues analysed postmenopausal women with low BMD who were randomised to placebo (n = 50) or romosozumab 210 mg (n = 50) every month for 2 years.

Romosozumab led to rapid and marked increases in BMD during year 1 for lumbar spine (11.4% vs -0.1%; P < .05) and total hip (4.2% vs -0.7%; P < .05) compared with placebo. These benefits were sustained into year 2 of the study (15.2% vs 0.4%; P < .05 and 5.5% vs -1.5%; P < .05, respectively).

Romosozumab induced rapid stimulation of bone formation (P1NP) and decreased bone resorption (CTX). Increases in P1NP were transitory, returning toward baseline within 6 to 12 months and remaining below baseline through year 2; CTX remained below baseline through year 2.

After completing treatment with romosozumab, women were randomised to receive denosumab 60 mg every 6 months or placebo for year 3 of the study.

In women receiving placebo after romosozumab, BMD decreased to almost baseline levels within 1 year, while women receiving denosumab had increases in lumbar spine and total hip BMD with were 19.4% and 7.1% greater than baseline levels, respectively.

P1NP and CTX levels were maintained following an initial increase among the women in the denosumab group, whereas levels among women in the placebo group were significantly reduced to levels below baseline.

Adverse events were similar for romosozumab and placebo groups.

“The frequency of injection site reactions and the development of antibodies remained very low with romosozumab therapy,” said Dr. McClung.

Funding for this study was provided by Amgen Inc. and UCB Pharma.

WCO is sponsored by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

**Strontium Ranelate Continues Efficacy for Osteoporosis Treatment After Long-term Bisphosphonate Use**

Abril 1, 2015
Follow-up Treatment of Osteoporosis with Strontium Ranelate after Long-Term Bisphosphonate Therapy.

By Chris Berrie

MILAN, Italy -- April 1, 2015 -- Strontium ranelate follow-up treatment after long-term oral bisphosphonate for patients with osteoporosis provides continued efficacy with significant benefits compared with a drug holiday, and demonstrates no safety concerns, according to results of a prospective, open-label study presented at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO).

“Strontium ranelate is an interesting candidate for the increasing number of patients where bisphosphonate treatment has to be stopped for adverse events or too-long application,” noted lead investigator Johann D. Ringe, MD, West German Osteoporosis Centre, Klinikum Leverkusen, University of Cologne, Leverkusen, Germany, speaking here on March 27. Long-term bisphosphonate antiresorptive therapy for patients with osteoporosis is associated with increased risk of osteonecrosis of the jaw and atypical femoral fractures.

Strontium ranelate treatment in women with postmenopausal osteoporosis has shown that its simultaneous anabolic effect on osteoclasts and inhibitory effect on osteoclasts can provide efficient reversal of the negative bone balance in these patients. Strontium ranelate can increase bone mineral density (BMD) in male patients with osteoporosis.

Dr. Ringe and colleagues investigated the use of strontium ranelate as follow-up treatment in female postmenopause and male primary osteoporosis patients after 4 to 6 years of treatment with weekly alendronate 70 mg.

The pairwise allocation following this alendronate therapy included 264 patients who continued calcium 600 mg/day plus vitamin D 1,400 IU/day supplementation, with either no further active treatment (drug holiday; n = 132) or with the addition of strontium ranelate 2 g/day (active treatment; n = 132), for 2 years.

The primary endpoint was mean percentage changes in lumbar spine and total hip bone mineral density (BMD) after 12 and 24 months.

For the drug-holiday group, the researchers observed negative lumbar spine and total hip BMD changes at month 12 (0.4%, -1.1%) and month 24 (-3.3%, -2.6%; P < .05), compared with continued significant positive benefits observed in the active-treatment group at month 12 (5.3%, 2.3%; P < .03) and month 24 (8.4%, 3.7%; P < .01).

When these drug-holiday and active-treatment BMD changes were compared directly, strontium ranelate showed significant benefits in all cases (P < .03 at least).

The team also compared the drug-holiday group with the active-treatment group over the 2 years of follow-up for some secondary endpoints: mean number of falls per patient year.
showed numerical benefit for active treatment (26 vs 18 falls); mean back pain scores (visual analogue scale) showed significant benefit for active treatment (3.9 vs. 1.8; P < .01); and total incidence of new fractures showed significant benefit for active treatment (34 vs. 22 fractures; P < .02).

The safety analysis demonstrated that both groups were similar. “We documented 54 and 60 adverse events, respectively, with no differences regarding thrombosis or cardiovascular events,” said Dr. Ringe.

Baseline characteristics for both groups were similar. The overall mean age was 67 years, and 75% of patients were female. In all, there was a mean of 5.2 years duration of previous oral bisphosphonates.

WCO is sponsored by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).

**Odanacatib Reduces Fracture Risk in Postmenopausal Women With Osteoporosis**

Marzo 31, 2015

[Presentation title: Odanacatib Anti-Fracture Efficacy and Safety in Postmenopausal Women With Osteoporosis: Results From the Phase 3 Long-Term Odanacatib Fracture Trial (LOFT). Abstract OC1]

By Chris Berrie

MILAN, Italy -- March 31, 2015 -- Odanacatib is generally well tolerated and significantly reduces osteoporotic fracture risk versus placebo in women with postmenopausal osteoporosis, according to a study presented here at the World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO).

Michael R. McClung, MD, Oregon Osteoporosis Center, Portland, Oregon, presented the findings on March 29 from the long-term odanacatib fracture trial (LOFT).

“We evaluated the effects of odanacatib therapy on fracture risk and safety in postmenopausal women with osteoporosis,” he said.

The study included 16,713 women who were randomised to placebo (n = 8,028) or oral odanacatib 50 mg/week (n = 8,685). All patients received vitamin D (5,600 IU/week) plus calcium (1,200 mg/day).

After the first interim analysis, a recommendation was made to stop the trial based on evidence of robust efficacy and favourable risk-benefit for odanacatib versus placebo.

The first primary endpoint was radiographically assessed morphometric vertebral fractures. When compared with placebo, odanacatib provided significant benefit from the first 6 months (1.3% vs 0.5%; hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.28-0.61). This was
maintained to end of study at 60 months (11.5% vs 6.3%; HR, 0.46; 95% CI, 0.40-0.53), for a significant relative risk reduction of 54% (P < .001).

Odanacatib provided significant relative risk reductions in hip fractures (47%; P < .001), clinical vertebral fractures (72%; P < .001), and non-vertebral fractures (23%; P < .001).

“The longer patients were on therapy, the greater was the observed reduction in non-vertebral fracture risk,” noted Dr. McClung.

Compared with placebo, odanacatib provided increases in bone mineral density (BMD) for lumbar spine (11.2% difference; P < .001), total hip (9.5% difference; P < .001), as well as sustained decreases in markers of bone resorption and early reduction in bone formation markers that returned to pre-treatment levels.

Diarrhoea and pain in the extremities were common in patients receiving odanacatib; however, these were generally mild.

There were indications in increased cerebrovascular events with odanacatib versus placebo (0.2% vs 0.1%; HR, 2.41). However, due to the large amount of missing data for this cerebrovascular analysis, a blinded-to-treatment re-adjudication of all cardiovascular events is being undertaken.

Funding for this study was provided by Merck & Co., Inc.

WCO is sponsored by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO).