Bone-forming Agents

a report by
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Peptides From the Parathyroid Hormone Family

Peptides from the parathyroid hormone (PTH) family have been investigated in the management of osteoporosis for over 30 years.[1] A continuous endogenous production or exogenous administration of PTH, as is the case in primary or secondary hyperparathyroidism, can lead to deleterious consequences on the skeleton, particularly on cortical bone. However, intermittent administration of PTH (e.g. through daily subcutaneous injections) results in an increase in the number and activity of osteoblasts, leading to an increase in bone mass and an improvement in skeletal architecture in both the trabecular and cortical skeleton. This treatment also increases cortical bone width.

The full length (1–84) molecule and the 1–34 N-terminal fragment are currently used for the management of osteoporosis. Based on their respective molecular weights, the equivalent dose of 1–34 fragment, relative to the 1–84 molecule, is 40% (e.g. 20µg and 40µg of 1–34 PTH is equivalent to 50µg and 100µg of 1–84 PTH, respectively).

In order to assess the effects of the 1–34 N-terminal fragment of PTH on fractures, 1,637 post-menopausal women with prior spine fractures were randomly assigned to receive 20µg or 40µg of 1–34 PTH or placebo, subcutaneously self-administered daily. Spine radiographs were obtained at baseline and at the end of the study (median duration of observation, 21 months) and serial measurements of bone mass were performed by dual-energy X-ray absorptiometry (DXA).

New spine fractures occurred in 14% of the women in the placebo group and in 5% and 4% of the women in the 20- and 40-µg dose groups, respectively. The relative risk of fracture compared with the placebo group was 0.35 and 0.31 (95% confidence interval (CI), 0.22–0.55 and 0.19–0.50), respectively. New non-spine fractures occurred in 6% of women in the placebo group and 3% of those in each PTH group (relative risk (RR), 0.47 and 0.46; 95% CI, 0.25–0.88 and 0.25–0.86, respectively). PTH had only minor side effects (occasional nausea and headache).[2]

The anti-fracture efficacy of PTH on spine fracture was not modulated by the age of the subjects (<65 years of age, 65–75 years of age or >75 years of age), prevalent spinal bone mineral density (BMD) values (T-score <-2.5 or >-2.5) or number of prevalent fractures (one, two or more fractures).[3]

At the end of this trial, patients were followed for an additional 18-month period without PTH, during which they were allowed to use any antiosteoporotic medication considered appropriate by their caregiver. Although the proportion of patients having received an inhibitor of bone resorption was slightly higher in patients previously in the placebo group than in the patients having received 20µg/day PTH, the reduction of spine fractures observed in this particular group during the initial trial was confirmed during this 18-month period (RR, 0.59; 95% CI, 0.42–0.85).[4] A follow-up in 1,262 women was conducted up to 30 months after discontinuation of treatment. The hazard ratio (HR) for combined teriparatide groups (20µg and 40µg) for the 50-month period after baseline was 0.57 (95% CI, 0.40–0.82), suggesting a sustained effect in reducing the risk of non-spine fragility fracture.[5]

Full-length recombinant human PTH (1–84) has also been investigated in the management of post-menopausal osteoporosis. It has been postulated that the C-terminal region of PTH, which teriparatide lacks, also has biological functions in the bone that are mediated by a novel receptor, specific for this region of the hormone. Teriparatide, for instance, has been associated with osteosarcoma in rats treated with massive doses during most of their lifespan, possibly related to its anti-apoptotic effects on bone cells and decrease in production of C-terminal PTH fragments. In contrast, researchers suggest that PTH (1–84) is likely to not have such effect due to the pro-apoptotic effects of C-terminal PTH fragments, which maintain normal bone cell turnover.[6,7] In a phase II study, women self-administered PTH (50µg, 75µg or 100µg) or placebo by daily subcutaneous injection for 12 months. The 100µg dose increased BMD significantly at three months and 12 months (+7.8%). Bone area also significantly increased (+2.0%). Non-significant decrease (-0.9%) in total hip BMD occurred during the first six months with the 100µg dose, but this trend reversed (+1.6%) during the second six months. Bone turnover markers increased during the first half of the study and were maintained at elevated levels during the second six months. Dose-related incidences of transient hypercalcaemia occurred, but only one

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patient (100µg group) was withdrawn because of repeated hypercalcaemia.[8,9] Results from the pivotal phase III studies have not yet been published as full papers. Evidence from the Treatment of Osteoporosis with Parathyroid Hormone (TOP) study, including women with low BMD (with or without previous fracture), suggest that PTH (1–84) reduced the incidence of vertebral fractures in all patients and prevented the incidence of first vertebral fracture in women with post-menopausal osteoporosis.[7] Reduction of non-vertebral or hip fractures does not clearly appear from the currently available data.

Strontium Ranelate

It has been suggested that strontium ranelate may inhibit bone resorption and stimulate bone formation, suggesting that, for the first time, a chemical entity used in the treatment of osteoporosis could be targeted to an uncoupling of the bone remodelling process.

The effects of strontium ranelate in post-menopausal women with spinal osteoporotic fractures were assessed during a double-blind, placebo-controlled trial – phase II Strontium Administration for Treatment of Osteoporsis Study (STRATOS). Either strontium ranelate (500mg, 1g or 2g/day) or placebo was given to 353 Caucasian women (66 years of age; lumbar BMD by DXA: 0.699g/cm^2). All of the patients were also given a daily supplement of calcium (500mg) and vitamin D2 (800IU). During the second year of treatment, the dose of 2g was associated with a 44% reduction (RR, 0.56; 95% CI, 0.35–0.89) in the number of patients experiencing a new spine deformity. Bone histomorphometry showed no mineralisation defects. The same percentage of withdrawals following an adverse effect (10%) was observed for patients receiving placebo and for those receiving strontium ranelate 2g.[10] The 2g dose of strontium ranelate per day was chosen for the phase III studies to confirm the anti-fracture efficacy of strontium ranelate in the treatment of post-menopausal osteoporosis.

Strontium ranelate has been investigated in a large phase III programme that includes two extensive clinical trials for the treatment of severe osteoporosis: Spinal Osteoporosis Therapeutic Intervention (SOTI), aimed at assessing the effect of strontium ranelate on the risk of spine fractures, and Treatment of Peripheral Osteoporosis (TROPOS), which aims to evaluate the effect of strontium ranelate on non-spine fractures. Both studies were multinational, randomised, double-blind and placebo-controlled with two parallel groups (strontium ranelate 2g/day versus placebo), a study duration of five years and the main statistical analysis planned after three years.

All patients included in these two studies had previously participated in a normalisation of calcium and vitamin D study called Fracture International Run-in Strontium Ranelate Trials (FIRST). Throughout the studies, the patients received calcium/vitamin D supplements that were individually adapted according to their deficiencies (500mg or 1000mg of calcium, and 400IU or 800IU of vitamin D3). From more than 9,000 osteoporotic post-menopausal women having taken part in FIRST, 1,649 patients were included in SOTI, with a mean age of 69 years, and 5,091 patients were included in TROPOS, with a mean age of 77.[11]

The primary analysis of the SOTI study, evaluating the effect of strontium ranelate 2g on spine fracture rates, revealed a 41% reduction in RR of experiencing a first new spine fracture throughout the three-year study, compared with placebo (139 patients with spine fracture versus 222, respectively) (RR, 0.59; 95% CI, 0.48–0.73), in the intent-to-treat population). This anti-fracture efficacy of strontium ranelate was demonstrated from the first year, with a 49% reduction in RR of experiencing a first new fracture with strontium ranelate compared with placebo (RR, 0.51, 95% CI, 0.36–0.74). Bone-specific alkaline phosphatase increased while serum CTX decreased. Lumbar BMD increased by 14.4% in the treated group when compared with the placebo group at three years. Strontium ranelate was well tolerated, without any specific adverse events, and no deleterious effects were observed on rates of non-spine fractures.[12]

The primary analysis of the peripheral study, evaluating the effect of 2g/day of strontium ranelate on non-spine fracture, showed that, in the entire sample, RR was reduced by 16% for all non-spine fractures (RR, 0.84; 95% CI, 0.70–0.99), and by 19% for major non-spine fractures (hip, wrist, pelvis and sacrum, ribs and sternum, clavicle, humerus; RR, 0.81; 95% CI, 0.66–0.98) in strontium ranelate-treated patients in comparison with the placebo group. In a post-hoc analysis requested by the European Committee for Medicinal Products for Human Use (CHMP), including 1,977 women at high risk of hip fracture (≥74 years of age and femoral neck BMD T score ≤-3, corresponding to -2.4 according to the National Health and Nutrition Examination Survey reference), the RR reduction for hip fracture was 36% (RR, 0.64; 95% CI, 0.41–0.99). RR of spine fractures was reduced by 39% (RR, 0.61; 95% CI, 0.51–0.73) in the 3,640 patients with spinal X-rays and by 45% in the subgroup without prevalent spine fracture (RR, 0.55; 95% CI, 0.39–0.77). Strontium ranelate increased BMD throughout the study, reaching +8.2% and +9.8% for femoral neck and total hip, respectively, at three years (p<0.001). The incidence of adverse events (AEs) was similar in both groups.[13] ■

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