report. In other words, the conclusions apply to the presented population of patients, and generalisations could be misleading. For instance, severe renal involvement seems to be rare in the black population in South Africa (2). There is, however, little doubt about the main message in Dr. Steen's report regarding the value of early aggressive treatment with ACE inhibitors, which have improved the long term outcome substantially, even among patients with advanced renal insufficiency. A survey of 332 such patients in 1990 showed only a 36% 3-year survival rate. Rheumatologists as well as dermatologists and other physicians seeing patients with suspected or established scleroderma have a great responsibility in recognising the earliest signs of severe renal involvement. Aggressive therapy, mainly with ACE inhibitors, does change the course and save lives. Whether all patients should be instructed to self-monitor their blood pressure may need some qualification. Also, the most severe form of SRC is not hypertensive (1). But the kidneys in a majority of all scleroderma patients suffer from impaired functional reserve, which is why over treatment is unlikely (4).

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Daily injections of parathyroid hormone increase bone mineral density and reduce the risk of vertebral and non-vertebral fractures in post-menopausal women

Authors: R.M. Neer *et al.*
Title: Effect of parathyroid hormone (1-34) on fractures and bone mineral density in post-menoupasal women with osteoporosis
Source: *N Engl J Me*d 2001; 344: 1434-41

Aim

Daily subcutaneous injections of parathyroid hormone or its aminoterminal segments have potent anabolic effects on bone without inducing hypercalcemia. In order to assess the effects of recombinant human PTH 1-34 on BMD and on vertebral and non-vertebral fractures, a multicenter, randomized, double-blind, placebo controlled trial was conducted. The study was stopped earlier than planned due to the decision of the sponsor.

Methods

1,637 post-menopausal ambulatory women with at least one moderate or two mild atraumatic vertebral fractures at screening, who had entered menopause at least 5 years before the beginning of the study, were enrolled at 99 centers in 17 countries. For women with fewer than two moderate fractures, an additional criterion was hip or spine bone mineral density (BMD) at least 1.0 SD below the T score.

All women received daily supplements of 1 g calcium and 400 to 1200 UI vitamin D and were randomly assigned to self-administered daily subcutaneous injections of placebo (544 women), or 20 mg (541 women) or 40 mg (552 women) of PTH 1-34. Serum calcium before and 4 to 6 hours after the injection and 24-hour calcium and creatinine excretion were measured at baseline and after 1, 6, 12 and 24 months of treatment. If the post-injection serum calcium was high or if urinary calcium exceeded 350 mg per day, and if the increase persisted, the calcium supplement was stopped permanently or the volume of the study drug was halved until the abnormality disappeared.

All women underwent radiography of the thoracic and lumbar spine at the baseline and at the end of the study. Each vertebra was graded as normal, or mildly, moderately or severely deformed and new vertebral fractures were registered. Non-vertebral fractures were documented by review of radiographs and classified as fragility fractures if not caused by an efficient trauma.

Lumbar BMD was measured in all women at baseline, at 12 and 18 months, and at the end of the study; proximal femoral BMD was measured in all women at baseline, at 12 months and at the end of the study. Forearm and total body BMD were assessed in a group of women at baseline, at 12 months and at the end of the study. Height was measured at baseline and every 12 months. Blood counts, serum chemical tests and urinalysis were performed at baseline and at 1,6,12, and 24 months. Serum antibodies to PTH 1-34 were performed at baseline and at 3, 12 and 24 months.

Results

The mean duration of study treatment in the groups receiving placebo, PTH 1-34 20 mg and 40 mg was 18 ± 5, 18 ± 6 and 17 ± 6 months, respectively.

Baseline and follow-up radiographs were available in 1327/1637 women (81%). In 105 of them, one or more new vertebral fractures occurred. With respect to placebo, PTH 1-34 20 mg and 40 mg reduced the risk of one or more vertebral fractures by 65% and 69%, respectively. The relative risks of fracture in the 20 mg and 40 mg were 0.35 and 0.31, respectively compared to the placebo group (95% confidence intervals, 0.22 to 0.55 and 0.19 to 0.50). The mean loss in height was greater in the placebo group than in the 20 mg and 40 mg PTH 1-34 groups ($p = 0.002$).

Both total new non-vertebral fractures and new non-vertebral fragility fractures occurred more in the placebo group than in the 20 mg and 40 mg PTH 1-34 groups ($P < 0.05$ in all cases). New non-vertebral fractures were found in a total of 119 women. Fifty-three (10%) had a fracture in the placebo group, 34 (6%), and 32 (6%) in the 20 mg and 40 mg PTH 1-34

groups, respectively. New non-vertebral fractures were considered fragility fractures in 58 women. Thirty women (6%) had a fragility non-vertebral fracture in the placebo group, and 14 (3%) in both PTH 1-34 groups. The relative risk for fragility fractures was 0.47 for the placebo group and 0.46 for both PTH 1-34 groups, respectively (95% confidence interval, 0.25 - 0.88 and 0.25 - 0.86).

As compared with placebo, 20 mg and 40 mg PTH 1-34 increased lumbar BMD by 9.7 ± 7.4% and 13.7 ± 9.7%, respectively; femoral neck BMD by 2.8 ± 5.7% and 5.1 ± 6.7%. These differences were all highly significant ($P < 0.001$). Both doses of PTH 1-34 increased total body BMD by 2% – 4% more with respect to placebo ($P < 0.001$). 40 mg PTH 1-34 significantly decreased BMD at the radius (-3.2 ± 4.5 with respect to placebo; $P < 0.001$).

No osteosarcoma, cardiovascular disorders, urolithiasis or gout developed during the study. Cancer developed in 40 women, with a higher incidence in the placebo group (4%) than in the 20 mg and 40 mg PTH 1-34 groups (2% in both groups) ($P < 0.05$ in both groups). 126 women withdrew from the study due to adverse events, 32 (6%) from the placebo group, 35 (6%) from the 20 mg group and 59 (11%) from the 40 mg group. Mild hypercalcemia was reported in 2% of the women in the placebo group, and in 11% and 20% of the women treated with 20 mg and 40 mg PTH 1-34, respectively. Treatment was withdrawn for repeatedly elevated calcemia in one woman each from the placebo and 20 mg groups, and in 9 women from the 40 mg PTH group. Nausea and headache were reported in 18% and 13% of the women in the 40 mg group, respectively. These percentages were significantly higher ($p < 0.05$) than those reported in the placebo group (8% for both events), which were not different from those reported in 20 mg group. Antibodies to PTH were found in one woman in the placebo group, and in 15 and 44 women from the 20 mg and 40 mg PTH 1-34 groups, respectively.

Conclusions

Administration of PTH 1-34 causes a reduction in the risk of vertebral and non-vertebral fractures and increases lumbar, femoral and total body BMD with only minor side effects. 40 mg PTH 1-34 is more efficacious than 20 mg both in reducing fractures and in increasing BMD, but is more likely to produce side effects. This suggests that in humans PTH is a potent anabolic agent for the bone and is more effective both in increasing BMD and reducing fracture risks than anti-resorption agents such as bisphosponates and SERMs.

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Comment

The prevention of osteoporotic fractures is a worldwide health issue and new treatment options are being investigated with the aim of reducing morbidity, mortality and social costs. At present, subjects at risk of fragility fractures are usually treated with anti-resorptive agents, such as estrogen, bisphosphonates, selective estrogen-receptor modulators and calcitonin. These agents have been proved to reduce osteoclastic bone resorption without affecting osteoblasts, which gives the net effect of an increase of bone mineral density (by 1-7% in 3 years). Prospective, long-term clinical trials have also demonstrated – with the exception of estrogen – that these agents are also able to reduce the incidence of vertebral fractures (by 30-50% in 3 years); among them only risedronate and alendronate have been proved to reduce hip fractures (by 40-50% in 3 years).

Parathyroid hormone (1-34) is the first bone anabolic agent (i.e., with the capacity to directly stimulate osteoblasts) which has been shown to prevent osteoporotic fractures. PTH (1-34) restores bone strength by stimulating bone accrual at the periosteal and endosteal surfaces, thus thickening the cortices and existing trabeculae of the skeleton and perhaps increasing the number of the trabeculae and their connectivity.

As demonstrated in this study, daily injections of PTH (1-34) for a mean of 18 months increased the bone mineral density of the spine by 9.7-13.7%, and reduced the risk of new vertebral fractures by 65-69% and that of nonvertebral fractures by 53% in a high risk group of postmenopausal women. These results exceed those reported for all other treatments to date. There is now solid evidence that PTH (1-34) is a powerful agent for treating osteoporosis: PTH (1-34) has been successfully tested in different forms of osteoporosis, including postmenopausal osteoporosis, osteoporosis in men, and that following glucocorticoid treatment; it also prevents bone loss in estrogen-depleted women with normal bone mineral density. Furthermore, on the basis of the results

of this study, to attain similar effects the treatment period with PTH (1-34) could be shorter (e.g. 18 months) than that usual with anti-resorptive agents (at least 36 months, but in clinical practice many years). Prescribing a more effective therapy for less time may counterbalance the expected lower compliance of patients to daily injections of PTH than that experienced with, for example, oral bisphosphonates once a week, which is satisfactory. The administration route and the safety profile of PTH (1-34), the individual cost/benefit ratio, and the need for close monitoring of calcemia are issues that will certainly play a role in clinical practice.

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