The 2002 Osteoporosis Canada clinical guidelines committee reviewed the evidence for several classes of drugs that reduce bone resorption and inhibit bone formation. Anabolic therapies are capable of inducing new bone formation through an increase in bone modelling and remodelling. Human parathyroid hormone (hPTH) is an 84-amino acid peptide hormone that plays a key role in the maintenance of calcium homeostasis. hPTH binds to a target cell surface G-protein-coupled hPTH/hPTHrP receptor, which results in activation of adenylate cyclase and phospholipases and increased intracellular levels of cyclic AMP and calcium. Intermittent hPTH given by subcutaneous injection has been shown to exert potent anabolic effects on the skeleton. hPTH increases the rate of bone remodelling and results in a positive remodelling balance, leading to thicker osteons (structural units of remodelled bone). New bone formation occurs on quiescent surfaces and, as a result, trabecular architecture comes to more closely resemble normal bone. hPTH(1–34) induces new periosteal bone apposition, which results in the enlargement of the outer circumference of tubular bones such as the radius. This bone apposition results from decreased osteoblast apoptosis and enhanced differentiation of osteoblasts from preosteoblasts. Bisphosphonates preserve existing skeletal microarchitecture but do not restore it toward a more normal structure. Increases in bone mass with bisphosphonates are most likely due to enhanced secondary mineralization of preformed osteons.

Two forms of recombinant hPTH have been evaluated in clinical trials, hPTH(1–34) and the intact 84-amino acid form, hPTH(1–84). hPTH(1–34) is approved for the treatment of severe osteoporosis. hPTH(1–84), although not currently approved, has been evaluated in clinical trials. hPTH(1–84) includes a C terminus, which may have discrete biologic properties and may therefore have different biologic actions from hPTH(1–34).

In this article we present the results of our systematic review of the literature on the efficacy and safety of hPTH therapy.

Methods

The hPTH working group included members of the Osteoporosis Canada Clinical Guidelines Committee and scientific consultants with Osteoporosis Canada who have expertise in hPTH or in clinical epidemiology or both. This
review was approved by all members of the Clinical Guidelines Committee.

We included RCTs of at least 1-year duration that compared hPTH with a placebo or with an active comparator and involved 1 of 3 distinct populations: postmenopausal women with osteoporosis, postmenopausal women with corticosteroid-induced osteoporosis or men with osteoporosis. The primary outcome was the effect of hPTH(1–34) or hPTH(1–84) on either bone mineral density (BMD) or fractures. Secondary outcomes were back pain and quality of life.

The Cochrane Collaborative approach for identifying RCTs guided our search strategy.16 We searched MEDLINE, EMBASE, HTA, Current Contents and the Cochrane Controlled Trials Registry from 1966 to September 2005 (see online Appendix 1, available at www.cmaj.ca/cgi/content/full/175/1/52/DC1). Citations of relevant articles and reviews were examined to identify other potential trials. Two reviewers (A.C. and N.Z.) evaluated all titles and abstracts for eligibility. Full articles of relevant trials were obtained to make final judgments about inclusion.

The 2 reviewers independently abstracted data on study characteristics, results and methodologic quality. Data examined included study design, population, dose, treatment duration, percent change in BMD and the number of subjects with fractures. Volumetric BMD data and biochemical markers were not included as outcomes in this review, since they are not widely accepted as surrogate outcomes. Missing data were requested from study investigators or sponsors. We decided a priori not to pool the BMD and fracture data from the various trials since different hPTH preparations (i.e., hPTH[1–34] v. hPTH[1–84]) may have different modes of action, and doses may not be comparable. For example, 20 µg of hPTH(1–34) may be roughly equivalent to 50 µg of hPTH(1–84) on a molar basis, but differences in peptide length may cause differences in tissue absorption or receptor activation.4

RCTs were classified as level 1 (an RCT of adequate sample size, with blinding of subjects and assessors) or as level 2 (RCT that does not meet level 1 criteria, owing to a small sample or methodologic limitations).

Results and interpretation

A total of 655 potentially relevant citations were identified and screened (Fig. 1). Of these, 24 were potentially eligible. Twelve trials were subsequently excluded: one included premenopausal women,17 10 were a duplicate report, companion or follow-up of a primary RCT,15,18–20 and in one BMD outcomes were for less than a year.27 Twelve published RCTs were included in this review.28–39 Nine trials involved postmenopausal women (Table 1),28–34,36,39 of which one involved women with corticosteroid-induced osteoporosis (Table 2).34 Three trials involved men with osteoporosis (Table 3).35–37 Ten trials evaluated hPTH(1–34)29–31,33–39 and 2 trials hPTH(1–84).28,32

Two trials had losses to follow-up of over 20%.26,32 8 trials had losses between 5% and 20%,26,29,31,34,35,37–39 and 2 had less than 5%.32,36 Allocation concealment was adequately reported in 2 trials30,39 and unclear in the remaining trials. Seven trials were double-blind.28,31–33,36–38

hPTH in postmenopausal women

In a large trial comparing hPTH(1–34) with calcium and vitamin D among women with severe osteoporosis and prior fractures, Neer and associates found a significant reduction in new vertebral and nonvertebral fractures associated with hPTH (Table 1 and Table 4).31 With 20 µg and 40 µg of hPTH(1–34) the relative risk (RR) of new vertebral fractures was 0.35 (95% confidence interval [CI] 0.22–0.55) and 0.31 (95% CI 0.19–0.50) respectively (absolute risk reduction [ARR] 9%–10%). Treatment with 20 µg hPTH(1–34) resulted in a RR of 0.47 (95% CI 0.25–0.88) for nonvertebral fractures and an ARR of 3%. In other hPTH(1–34) trials, the absolute number of fractures was too small to achieve significance28,38,39 (Table 4). Body and associates found a reduction in nonvertebral fractures with 40 µg/d hPTH(1–34) compared with 10 mg/d alendronate (4.1% v. 13.7%, p = 0.042).33

Six trials compared the effect of hPTH(1–34) with placebo or an active comparator on BMD (Table 4). Doses of hPTH(1–34) ranged from 20 µg/d to 50 µg/d and treatment durations from 1 to 3 years. There was a consistent increase in lumbar spine and femoral neck BMD but little effect on BMD at the distal radius. Increases in lumbar spine BMD with hPTH(1–34) were significant and ranged from 9.7% to 10.3% with 20 µg/d and from 13.7% to 14.3% with 40 µg/d (Table 4). Changes in femoral neck BMD were significant but

![Fig. 1: Flow of articles through the systematic review. RCT = randomized controlled trial.](https://example.com/fig1.jpg)
smaller, ranging from 2.8% to 3.9% in the 20 µg/d group and 4.5%–5.1% in the 40 µg group.

Two trials compared the effect of hPTH(1–84) with that of placebo or alendronate. Increases in lumbar spine BMD ranged from 6.3% to 7.8% after one year with 50–100 µg of hPTH(1–84), which were larger but not significantly different than increases seen with alendronate.28,32 Increases in femoral neck BMD with hPTH(1–84) were small compared with placebo and less than that seen with alendronate (Table 4).

**hPTH compared with bisphosphonates**

Two trials compared hPTH(1–34) 20 µg or 40 µg with alendronate 10 mg/d in postmenopausal women.33,38 Body and associates compared 40 µg of hPTH(1–34) with alendronate 10 mg daily. Increases of lumbar spine and femoral neck BMD were greater with hPTH than with alendronate (p < 0.001). At the ultradistal radius the increase with alendronate was 1.4% compared with 0.23% with 40 µg hPTH(1–34) (p < 0.001).33

In a study by McClung and associates, hPTH(1–34) 20 µg/d resulted in significantly greater increases (10.3%) in lumbar spine BMD than with alendronate 10 mg/d.38

**Combination therapy**

Three trials evaluated hPTH therapy combined with either a bisphosphonate or calcitonin.29,30,32 In an RCT involving 238 postmenopausal women with osteoporosis, alendronate combined with hPTH(1–84) did not result in larger increases in lumbar spine BMD than with hPTH alone.32 Cosman and associates compared the effect of hPTH(1–34) 25 µg and hormone replacement therapy (HRT) with that of HRT alone in 52 postmenopausal women who had been taking HRT for at least a year.30 Three years of combination therapy resulted in increases in lumbar spine and total hip BMD of 13.4% and 4.4% respectively compared with a nonsignificant increase with HRT alone. In a small 2-year RCT, Hodsman and associates compared cyclical hPTH(1–34) 50 µg followed by placebo calcitonin with hPTH followed by sequential salmon calcitonin (Table 1). Combined sequential therapy with calcitonin did not offer any benefits for BMD over cyclical hPTH alone.29

### Table 1: Characteristics of trials of human parathyroid hormone (hPTH) involving postmenopausal women

| Study                  | No. of patients (treatment/control) | Study duration | Patient characteristics | Intervention | Outcome measures | Loss to follow-up and study limitations |
|------------------------|-------------------------------------|----------------|--------------------------|--------------|------------------|----------------------------------------|
| Hodsman et al., 2003   | 217 (162/55)                        | 1 yr           | • Mean age 64.5 (SD 6.0) y | hPTH(1-84), 50 µg, 75 µg and 100 µg subcutaneously v. placebo daily | • BMD and BMC: LS, FN, total hip and total body | 11/217 (5.1%) lost to ITT analysis, 31/217 (14.3 %) lost overall No fracture data |
| Cosman et al., 2001    | 52 (27/25)                          | 3 yr           | • Mean age 60.2 (SD 1.6) y | hPTH(1-34) 25 µg + HRT v. HRT alone; HRT 0.625 mg Premarin or 50 µg Estraderm and 5-10 mg progestin daily for 10 d or 2.5 mg/d | • BMD: LS, total hip and total body | 6/52 (11.5%) Small sample No fracture data |
| Neer et al., 2001      | 1637 (1093/544)                     | 1.5 yr         | • Mean age 69.3 (SD 7.0) y | Human recombinant PTH(1-34) 20 µg, 40 µg v. placebo | • BMD: LS, FN, trochanter, total hip, radius and total body | 311/1637 (19.0%) No fracture data |
| Black et al., 2003/2005| 238 (178/60)                        | 2 yr           | • Mean age 69.9 (SD 7.1) y | hPTH(1-84) 100 µg v. PTH 100 µg + alendronate 10 mg v. alendronate 10 mg | • BMD: LS, FN, total hip and 1/3 distal radius | 11/238 (4.6%) Not powered to evaluate fractures |
hPTH therapy after prior bisphosphonate therapy

Although the anabolic effects of hPTH may be accentuated if bone resorption is suppressed, there is concern that the decreased remodelling rates induced by bisphosphonates might impair the ability of hPTH to stimulate new bone formation.

In contrast, Cosman and associates randomly assigned women who had previously taken alendronate to either cyclic or daily hPTH(1–34) in combination with alendronate or to alendronate alone. Significant increases in lumbar spine BMD of 6.1% and 5.4% were noted in the daily and cyclic treatment arms respectively.

Sequential use of bisphosphonate therapy after cessation of hPTH

After hPTH(1–34) is discontinued, BMD declines; this loss can be prevented with sequential use of a bisphosphonate.

In an RCT of hPTH(1–84) and alendronate, Black and associates randomly assigned women to receive a second year of either alendronate or placebo and found that the alendronate group had significant increases in lumbar spine BMD (4.9%) compared with controls (−1.7%) (p < 0.01).

Summary

There is level 1 evidence that hPTH(1–34) 20 µg/d and 40 µg/d increase BMD at the lumbar spine and proximal femur and decrease the risk of both vertebral and nonvertebral fractures in postmenopausal women with prior vertebral fractures. The effect of hPTH(1–34) on hip fractures has not been assessed. hPTH(1–34) results in larger increases in lumbar spine BMD than alendronate. There are no head-to-head fracture trials that compare the efficacy of 20 µg of hPTH(1–34) to bisphosphonates in decreasing the risk of fracture.

There is level 1 evidence that hPTH(1–84) increases lumbar spine BMD in postmenopausal women with osteoporosis. The small increase in femoral neck BMD and decline in total body BMD may reflect a transient imbalance between cortical remodelling and bone formation. The decline in BMD at the distal radius seen in hPTH trials is not felt to be indicative of decreased bone strength and may occur as a result of the increased

Table 1: Characteristics of trials of human parathyroid hormone (hPTH) involving postmenopausal women (continued)

| Study          | No. of patients (treatment/control) | Study duration | Patient characteristics | Intervention                                                                 | Outcome measures                                                                 | Loss to follow-up and study limitations |
|----------------|-------------------------------------|----------------|-------------------------|-------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------|
| Body et al, 2002 | 146 (73/73)                          | 14 mo          | • Mean age 65.5 (SD 8.5) yr
• Postmenopausal 18.5 (SD 9.5) yr
• T-score: FN –3.4 (SD 1.1) | hPTH(1–34) 40 µg + placebo tablet v. alendronate 10 mg + placebo injection
• Calcium 1000 mg/d, vitamin D 400–1200 IU/d | BMD/BMC: LS, FN, 1/3 radius, ultradistal radius and total body
• Fracture: nonvertebral
• Back pain | 38/146 (26.0%) Fractures were secondary outcome |
| Hodsman et al, 1997 | 39                                  | 2 yr           | • Mean age 67.0 (SD 8.0) yr
• Fracture prevalence 100%
• T-score: LS –3.3 (SD 1.3), FN –3.3 (SD 1.1) | hPTH(1–34) sequential 50 µg (28 d) v. hPTH(1–34) sequential 50 µg (28 d) + calcitonin 75 µg (42 d)
• Calcium 500 mg/d (20-d cycles) | BMD: LS, FN
• Fractures: vertebral and nonvertebral | 9/39 (23.1%) Small sample |
| McClung et al, 2005 | 203 (102/101)                       | 18 mo          | • Mean age 65.9 yr
• Postmenopausal 19.7 yr
• T-score: LS –2.8 (SD 0.7) | hPTH(1–34) 20 µg v. alendronate 10 mg/d
• Calcium 1000 mg/d, vitamin D 400–800 IU/d | BMD: LS
• Back pain | 31/203 (15.2%) Unable to provide data on comparative fracture rates; radiographs of spine not done |
| Cosman et al, 2005 | 126 (43/40/43)                      | 15 mo          | • Mean age 68.4 (SD 7.6) yr
• Postmenopausal 20.8 yr
• Fracture prevalence 48%
• T-score: LS –2.9 (SD 0.9) | hPTH(1–34) 25 µg/d + alendronate 70 mg/wk v. hPTH(1–34) cyclic (25 µg/d for 3 mo, then none for 3 mo) + alendronate 70 mg/wk v. alendronate 70 mg/wk
• Calcium supplementation for total intake of 1200-1500 mg/d, vitamin D supplementation to increase 25(OH)D intake to > 50 nmol/L | BMD: LS and total hip
• Fractures: vertebral and clinical nonvertebral | 18/126 (14.3%) Not powered to evaluate fractures |

Note: SD = standard deviation, LS = lumbar spine, FN = femoral neck, BMD = bone mineral density, BMC = bone mineral content, ITT = intention to treat, HRT = hormone replacement therapy.
width of the radius. The absence of head-to-head fracture data suggests that hPTH(1–34) be limited to patients at high risk of fractures by virtue of very low BMD and pre-existing fractures.

There is level 1 evidence that combination therapy with alendronate and hPTH(1–84) may blunt the anabolic effect of hPTH on BMD. There are no fracture data comparing the effect of the combination of hPTH and alendronate with that of hPTH alone.

hPTH(1–34) in postmenopausal women with corticosteroid-induced osteoporosis

Lane and associates evaluated the effect of hPTH(1–34) in 51 postmenopausal women taking corticosteroids and HRT. Women were given hPTH(1–34) for one year and then followed for an additional year. hPTH(1–34) 25 µg in combination with HRT increased BMD by 12.6% at the lumbar spine and by 5.2% at the femoral neck after 2 years.34

Summary

There is level 2 evidence that hPTH(1–34) increases lumbar spine BMD in postmenopausal women with corticosteroid-induced osteoporosis. Fracture data are lacking in this population.

hPTH(1–34) in men with osteoporosis

Kurland and associates compared 25 µg hPTH(1–34) with placebo in a small trial involving men with idiopathic os-

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**Table 2:** Characteristics of trials of human parathyroid hormone (hPTH) involving men with osteoporosis

| Study                  | No. of patients (treatment/control) | Study duration | Patient characteristics | Intervention | Outcome measures | Loss to follow-up |
|------------------------|-------------------------------------|----------------|-------------------------|--------------|------------------|-------------------|
| Kurland et al,36 2000  | 23 (10/13)                          | 1.5 yr         | • Mean age 51.7 (SD 2.8) yr  
• Fracture prevalence 78%  
• T-score: LS < -2.5 | hPTH(1–34) 25 µg v. placebo  
• Calcium supplementation to increase daily intake to 1500 mg, vitamin D 400 IU/d | • BMD: LS, FN, total hip and 1/3 distal radius  
• Fracture: vertebral | 0/23 |
| Finkelstein et al,35 2003 | 83 (27/28/28)               | 2 yr           | • Mean age 57.7 (SD 8.0) yr  
• T-score: LS or FN < -2.0 | hPTH(1–34) 40 µg v. hPTH(1–34) 40 µg + alendronate 10 mg v. alendronate 10 mg alone  
• Calcium supplementation to increase daily intake to 1000-1200 mg, vitamin D 400 IU/d | • BMD: posterior-anterior spine, lateral spine, FN, total hip, radial shaft and total body  
• QCT: spine | 10/83 (12.0%) |
| Orwoll et al,37 2003   | 437 (290/147)                      | 11 mo          | • Mean age 58.6 (SD 13.0) yr  
• T-score: LS -2.2 (SD 1.2), FN -2.7 (SD 0.8) | hPTH(1–34) 20 µg and 40 µg v. placebo  
• Calcium 1000 mg/d, vitamin D 400-1200 IU/d | • BMD: LS, FN, trochanter, total hip, distal radius, ultra-distal radius and total body  
• Fracture: nonvertebral | 81/437 (18.5%) |

Note: SD = standard deviation, LS = lumbar spine, BMD = bone mineral density, SE = standard error of the mean, FN = femoral neck, QCT = quantitative computed tomography.

**Table 3:** Characteristics of trial of human parathyroid hormone (hPTH) involving postmenopausal women taking corticosteroid therapy

| Study                  | No. of patients (treatment/control) | Study duration | Patient characteristics | Intervention | Outcome measures | Loss to follow-up |
|------------------------|-------------------------------------|----------------|-------------------------|--------------|------------------|-------------------|
| Lane et al,20,34 1998/2000 | 51 (28/23)                         | 2 yr           | • Mean age 62.7 (SD 9.9) yr  
• Postmenopausal 17.9 (SD 9.9) yr  
• Fracture prevalence 27.5%  
• T-score: -2.8 (SD 0.17) | hPTH(1–34) 25 µg + HRT + prednisone v. HRT + prednisone  
• Calcium supplementation to increase daily intake to 1500 mg, and vitamin D 800 IU/d | • BMD: LS, FN, trochanter, total hip and 1/3 distal radius  
• Fractures: vertebral and nonvertebral | 3/51 (5.9%) |

Note: SD = standard deviation, LS = lumbar spine, HRT = hormone replacement therapy, BMD = bone mineral density, FN = femoral neck.
teoporosis. After 18 months, BMD had increased significantly by 13.5% and 2.9% at the lumbar spine and femoral neck respectively. Total hip BMD did not change significantly, and there was a significant decrease at the 1/3 distal radius (−1.2%). Orwoll and associates, in an RCT involving 437 men with low BMD, compared 20 µg or 40 µg of hPTH(1–34) with calcium and vitamin D. Of these men, 49% had hypogonadism. After one year, lumbar spine BMD increased by 5.4% with 20 µg and by 8.5% with the 40 µg dose compared with no change with placebo. There was a nonsignificant decrease in nonvertebral fractures with hPTH(1–34) compared with placebo. Finkelstein and associates compared hPTH(1–34) 40 µg alone, hPTH(1–34) alone. Increases in lumbar spine and femoral neck BMD were 18.1% and 9.7% respectively in group receiving hPTH(1–34) with alendronate 10 mg/d, and alendronate alone. There was a nonsignificant decrease in nonvertebral fractures with hPTH(1–34) compared with placebo. In 2 trials comparing hPTH(1–34) 40 µg dose alone, and one trial hPTH(1–34) with alendronate 10 mg/d, and alendronate alone. Increases in lumbar spine and femoral neck BMD were 18.1% and 9.7% respectively in group receiving hPTH(1–34) and alendronate or alendronate alone (p < 0.001) (Table 4). Summary

There is level 1 evidence that hPTH(1–34) increases BMD at the lumbar spine and femoral neck in men with osteoporosis, but there is no data on fractures in this population.

Health-related quality of life and back pain

Neer and associates assessed health-related quality of life with both generic (Nottingham Health Profile) and disease-specific measures (Osteoporosis Assessment Questionnaire) (OPAQ). Using the OPAQ, fractures in a subgroup of 365 women were associated with a decline in health-related quality of life. However, there were no significant differences between patients taking hPTH(1–34) and those taking placebo. Back pain was reported in 3 hPTH(1–34) trials, and one trial had baseline and follow-up spine radiography. A significant reduction in back pain was seen among postmenopausal women in the fracture trial of hPTH(1–34). In 2 trials compar-

| Study            | hPTH dose (µg) | Comparator       | Level of evidence | Fractures, treatment v. control, % | BMD, treatment v. control, % change |
|------------------|---------------|------------------|------------------|-----------------------------------|-------------------------------------|
| McClung et al, 2005 | 20 (1–34)    | Alendronate      | 1 NA             | 8.8 v. 7.9                        | 10.3 v. 5.5†                        |
| Cosman et al, 2005 | 25 (1–34)    | Alendronate      | 2 NA             | 10.5 v. 5.9 v. 5.6†               | 6.1 v. 5.4 In graph only            |
| Body et al, 2002 | 40 (1–34)    | Alendronate      | 1 NA             | 4.1 v. 13.7‡                      | 14.3 v. 6.4†                        |
| Black et al, 2003 | 100 (1–34)   | Alendronate      | 1 NA             | NA                                | 6.3 v. 6.0 v. 4.54§                 |
| Neer et al, 2001 | 20–40 (1–34) | Placebo          | 1 NA             | 2.9 v. 6.4†                       | 13.7† v. 9.7** In 1.1†              |
| Hodsman et al, 2003 | 50–100 (1–34) | Placebo          | 1 NA             | 11.2 v. 8.9                       | 5.1** v. 2.8¶ v. -0.7†              |
| Hodsman et al, 1997 | 50 (1–34)    | Calcitonin       | 2 NA             | None in either arm                | 100-µg dose: 7.8 v. 0.9†            |
| Cosman et al, 2001 | 25 (1–34)    | HRT              | 2 NA             | 13.4 v. 1.5†                      | 100-µg dose: 0.5 v. -0.7             |
| Lane et al, 1998/2000 | 25 (1–34)   | HRT              | 2 NA             | 13.5 v. 0†                        | 4.7 v. 0‡ v. -3.3 v. 0              |
| Kurland et al, 2000 | 25 (1–34)    | Placebo          | 2 NA             | 2.9 v. 0‡                         | 12.4 v. 0.5‡                        |
| Orwoll et al, 2003 | 20–40 (1–34) | Placebo          | 1 NA             | 9.0± v. 5.8** v. 0.52†            | 2.9† v. 1.5** v. 0.3†              |
| Finkelstein et al, 2003 | 40 (1–34)    | Alendronate      | 2 NA             | 18.1 v. 14.8 v. 7.9¶ v. 3.2‡       | 9.7 v. 6.2 v. 3.2‡ v. 1.0‡           |

Note: NA = not assessed in the study, NR = not reported, HRT = hormone replacement therapy.

• hPTH (daily) + alendronate v. hPTH (cyclic) + alendronate v. alendronate alone.
• hPTH dose: 20 µg.
• hPTH v. hPTH + alendronate v. alendronate alone.
• hPTH dose: 40 µg.

* p < 0.05.
† p < 0.01.
‡ p < 0.001.
§ p < 0.5.
ing hPTH(1–34) and alendronate 10 mg, hPTH(1–34) was associated with a significant decrease in moderate to severe back pain.33,38 A meta-analysis of individual patient data from 5 trials comparing hPTH(1–34) with comparators found that patients taking hPTH(1–34) had a reduced risk of back pain (pooled RR 0.60, 95% CI 0.55–0.80).45

Summary

There is no evidence of improved health-related quality of life associated with hPTH(1–34) or calcium with vitamin D in postmenopausal women with osteoporosis. There is level 2 evidence that back pain may be reduced in patients given hPTH(1–34).

Adverse events

A potential safety issue with hPTH(1–34) is increased risk of osteosarcoma, which was reported in a life-long carcinogenicity study involving Fischer rats given high-dose hPTH(1–34) from infancy through senescence (8 weeks of age through 2 years).44 Because of this unexpected finding, trials of hPTH(1–34) for postmenopausal women with severe osteoporosis and men with osteoporosis31,33,37 were terminated prematurely by the sponsor. Osteosarcoma was found with all doses, and, in the lower-dose ranges, was first detected after about 20 months of therapy. There have been no reports of osteosarcoma in clinical trials, and although there are isolated case reports of osteosarcoma in patients with long-standing hyperparathyroidism, there is no evidence to suggest that osteosarcoma is of increased frequency in hyperparathyroidism.45,46

Adverse events were included in all trials, but reporting was variable. Nine hPTH(1–34) trials30,31,33–35 reported postdose hypercalciemia (serum calcium level > 2.6 mmol/L) that ranged from 3% to 11% among patients taking 20 µg of hPTH(1–34) and from 16.8% to 38% among patients taking 40 µg compared with 0%–3% among those taking the comparator.31,33 The overall pooled number of events of hypercalciemia was 282 in 1594 subjects from 7 trials. These episodes were mild; serum calcium levels usually returned to normal within 24 hours, and no clinical sequelae were reported in subjects with transient hypercalciemia. Hypercalciemia rates in the hPTH(1–84) trials ranged from 12% to 15.6%; there were 46 cases among patients taking hPTH out of a total of 340, compared with no cases among those taking the comparator.29,32

Transient hypercalciuria (24-hour urine collection showing calcium level of ≥ 8 mmol/d or urine calcium/creatinine ratio > 1.0) was reported in 6 hPTH(1–34) trials and ranged from 0% to 10% difference between hPTH and comparator.29,31,33,35,37,39 There were no reported increases in renal stones. A 10% increase in serum creatinine levels was reported in one trial but did not exceed the normal range.29 In another trial, increases in creatinine clearance were reported with hPTH that were nonsignificant compared with increase seen with placebo.26

The frequency of headaches among treatment subjects in hPTH(1–34) trials ranged from 8.1% to 10.8% and was not significantly greater than among control subjects.31,37 hPTH(1–34) 20 µg significantly increased the proportion of patients experiencing dizziness (3%)35 and leg cramps (range 2%–8%),31,37 with a higher proportion in the 40 µg treatment arm. Hyperuricemia was reported in 2 hPTH(1–34) trials32,37 and ranged from 0% to 3% of subjects. Hyperuricemia was associated with gout in 3 subjects taking hPTH(1–84).32

The proportion of subjects with serious adverse events was not significantly different between treatment arms. PTH treatment causes transient increases in serum calcium, but these episodes usually resolve. If they persist, they can be managed by decreasing calcium and vitamin D supplements.

This article has been peer reviewed.

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