Position paper of the National Osteoporosis Foundation of South Africa (NOFSA) on the use of parathyroid hormone (PTH 1-34) in the treatment of osteoporosis

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The mainstay of current therapies for osteoporosis is antiresorptive agents such as calcium, vitamin D, oestrogen, selective oestrogen receptor modulators (SERMs), calcitonin and the bisphosphonates. These drugs reduce but do not eliminate fracture risk, and do not restore lost bone structure. Anabolic agents have the potential to increase bone mineral density (BMD), restore skeletal micro-architecture and reduce fracture risk to a greater extent than the antiresorptives. Fluoride was the first anabolic agent to be used in the treatment of osteoporosis, followed by growth hormone and insulin-like growth factor. More recently, strontium, statins and parathyroid hormone (PTH) have been added to the list, with recombinant human PTH emerging as the most promising osteo-anabolic agent to date.[1]

Intermittent, low-dose PTH administration causes rapid stimulation of bone formation resulting in a marked increase in bone mass, size and strength, as well as improvements in trabecular micro-architecture (e.g. an increase in trabecular number, decrease in trabecular spacing and major improvements in histological indices of trabecular connectivity) and cortical geometry (e.g. an increase in cortical thickness, cross-sectional area and strength, despite a transient increase in endocortical porosity).[2-10] Following a number of smaller studies on the effects of PTH on fracture risk, the results of a large randomised placebo-controlled trial involving 1 637 women with postmenopausal osteoporosis were recently published.[11] Compared with placebo, daily subcutaneous injection of hPTH (1-34), for as little as 21 months, reduced the risk of new vertebral fractures by 65 - 70% and non-vertebral fractures by 35 - 40%. Favourable results on the effects of PTH on bone mass (BMD) and bio-markers of bone turnover have also been reported in male[12-14] and glucocorticoid-induced[15] osteoporosis.

Because PTH increases both bone formation and bone resorption, it was initially postulated that combining PTH with an antiresorptive agent would enhance its effect on bone mass and strength. Controlled, comparative studies to test this hypothesis are limited and confined to BMD and biomarker data. Whereas concomitant treatment with oestrogen (or a SERM) plus PTH does not appear to alter outcome,[4,15] the concurrent use of PTH and a more potent antiresorptive agent like alendronate has recently been shown to reduce the anabolic effects of PTH on BMD and biochemical markers of bone formation in both men[14] and women[16] with osteoporosis. Biomarkers of bone resorption increased in patients treated with PTH alone, and decreased in those treated with PTH plus alendronate. Longer-term studies employing fracture rate as primary endpoint are required to determine whether and how antiresorptive drugs can be used in conjunction with PTH. Limited data are also available on the skeletal response following discontinuation of PTH treatment. While some studies have suggested that BMD is maintained, others have shown that BMD decreases after PTH therapy is stopped.[17,18] Further studies are required to clarify this issue.

Side-effects of PTH have been limited to occasional nausea, headaches and leg cramps. Mild hypercalcaemia occurs in some 10% of patients receiving 20 µg PTH daily, but the incidence of hypercalciuria and renal stone disease does not appear to increase.[11] Serum uric acid levels may increase by up to 20%, but clinical gout has not been shown to be more prevalent in patients treated with PTH. Of some concern too is the tumorigenic potential of PTH. Long-term studies with high-dose PTH, administered to 6-week-old Fisher 344 rats, have demonstrated a dose-related increased risk of osteogenic sarcoma.[19,20] This effect is consistent with lifelong exposure, in a growing rodent, to high-dose PTH and is unlikely to have relevance to human bone physiology. Shorter or lower-dose exposure to PTH has not resulted in the development of osteosarcomas or other bone tumours. All primate studies have failed to show a similar association and osteogenic sarcomas do not occur with increased frequency in patients with primary hyperparathyroidism, nor were they noted in any of the clinical trials performed in over 2 500 patients treated with

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PTH (1-34) for up to 3 years.[19-22] It is, therefore, reasonable to conclude that PTH is safe in human subjects, although ongoing safety data need to be collated.

The need for a position paper on the use of PTH

PTH (1-34) or teriparatide will soon become available as a treatment option for osteoporosis in South Africa. The local cost of this product will undoubtedly be high (estimated at R50 000 per annum) and poses serious ethical dilemmas with regard to the allocation of expensive resources. Clear indications for its use, close audit of its appropriate and cost-effective utilisation and every effort to make this valuable drug available to all, have determined the need for this position paper, the methodology of which is delineated in Annexure A.

Indications for the use of PTH (1-34)

Whereas many potential indications for its use may exist (e.g. very low prevalent BMD, high fracture risk), we recommend that PTH (1-34) should only be used in patients with severe, established osteoporosis, i.e.:

1. A low BMD and two or more prevalent fractures, or

2. Failed antiresorptive therapy, i.e. after adhering to adequate antiresorptive therapy for 12 months or more, the patient experiences: (*i*) an incident fragility fracture; or (*ii*) unacceptable rate of bone loss (e.g. a decrease in vertebral BMD of ≥ 5% per annum) as documented on two or more consecutive follow-up BMD measurements.

Contraindications to the use of PTH (1-34)

The following are recommended absolute and relative contra-indications to the use of PTH:

Absolute

- Growing individuals (age < 25 years)
- Pregnancy and lactation
- Pre-existing hypercalcaemia
- Renal impairment (serum creatinine > 180 mmol/l)
- Marked increase (≥ 3 ×) in liver enzymes
- Neoplasm(s) in the previous 5 years
- Increased risk of osteosarcoma (e.g. prior skeletal radiation; Paget's disease of bone).

Relative

- Mild renal insufficiency (serum creatinine 120 - 180 mmol/l)
- Moderate increase (< 2 ×) in liver enzymes
- Possible osteomalacia
- Previous kidney stones
- Gout.

Dose and duration of PTH (1-34) therapy

We recommend that 20 µg PTH (1-34) per day should be used, for no longer than 18 months.

Patient selection, treatment and follow-up protocols

- Only patients subjected to a full clinical and laboratory work-up will be considered for treatment with PTH (1-34). Details of said assessment are depicted in Annexure B, but aim to confirm a diagnosis of osteoporosis and to rule out other causes of a low BMD (e.g. osteomalacia, primary hyperparathyroidism), rule out causes of secondary osteoporosis which may require treatment in their own right, evaluate the severity of the disease, and assess compliance and adherence to prior therapy for osteoporosis.

- Each application for PTH (1-34) treatment will be assessed by a working group consisting of senior council members of the National Osteoporosis Foundation of South Africa (NOFSA). These NOFSA councillors will be blinded to the identity of the primary care physician and will not be remunerated in any way for services rendered. A National Registry of patients treated with teriparatide will be established. Only patients who comply with the recommended indications for PTH (1-34) treatment will be considered. If clinical or biochemical assessment (increased biomarkers of bone turnover in the absence of a fracture in the preceding 3 months) suggest poor adherence to antiresorptive therapy, improved compliance will be required before treatment with PTH (1-34) is considered.

- Enrolled patients will receive daily supplements of 500 mg of elemental calcium and 400 - 800 IU of vitamin D. Given reports that concurrent use of PTH and alendronate may ameliorate the anabolic effects of PTH,[14,16] concomitant treatment with PTH plus antiresorptive agents is not recommended. If patients were previously treated with bisphosphonates these agents should therefore be discontinued before initiation of PTH therapy. A washout period, without active treatment, is not however deemed necessary in these patients, given the severity of their disease.

- Careful clinical follow-up of all subjects is required (see National Registry above). Serum and urine (24-hour) calcium levels should be monitored at 1, 6 and 12 months after starting PTH therapy. Assessment of lumbar and femoral BMD employing DEXA, and

vertebral morphometry employing standard spine X-rays, should be obtained at 9 and 18 months. The standard post-launch osteosarcoma surveillance programme, initiated and funded by the manufacturer (Eli Lilly), is mandatory for all patients.

- Following completion of the 18-month course of PTH (1-34) therapy, treatment with a potent antiresorptive agent (e.g. bisphosphonate) is recommended, to preserve bone mass gained.

1. Hough FS. New anabolic agents in the treatment of osteoporosis. *S Afr Med J* 2003; **8(2):** 44-45.
2. Tam CS, Heersche JN, Murray TM, Parsons JA. Parathyroid hormone stimulates the bone apposition rate independently of its resorptive action: differential effects of intermittent and continuous administration. *Endocrinology* 1982; **10:** 506-512.
3. Hirano T, Burr DB, Turner CH, *et al.* Anabolic effects of human biosynthetic parathyroid hormone fragment (1-34), LY333334, on remodeling and mechanical properties of cortical bone in rabbits. *J Bone Miner Res* 1999; **14:** 536-545.
4. Lindsay R, Nieves J, Formica C, *et al.* Randomised controlled study of effects of parathyroid hormone on vertebral bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997; **350:** 550-555.
5. Roe E, Sanchez S, Del Puerto G, *et al.* Parathyroid hormone (hPTH 1-34) and estrogen produce dramatic bone density increases in postmenopausal osteoporosis: results from a placebo-controlled randomised trial. *J Bone Miner Res* 1999; **14:** S137.
6. Body JJ, Gaich GA, Scheele WH, *et al.* A randomised double-blind trial to compare the efficacy of teriparatide with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 2002; 87: 4528-4535.
7. Zanchetta JR, Bogado CE, Ferretti JL, *et al.* Effect of teriparatide [recombinant human parathyroid hormone (1-34)] on cortical bone in postmenopausal women with osteoporosis. *J Bone Miner Res* 2003; **18:** 539-543.
8. Dempster DW, Cosman F, Kurland ES, *et al.* Effects of daily treatment with parathyroid hormone on bone microarchitecture and turnover in patients with osteoporosis: a paired biopsy study. *J Bone Miner Res* 2001; **16:** 1846-1853.
9. Marcus R, Wang O, Satterwhite J, Mitlak BH. The skeletal response to teriparatide is largely independent of age, initial bone mineral density, and prevalent vertebral fractures in postmenopausal women with osteoporosis. *J Bone Miner Res* 2003; **18:** 18-23.
10. Rubin MR, Cosman F, Lindsay R, Bilezikian JP. The anabolic effects of parathyroid hormone. *Osteoporosis Int* 2002; **13:** 267-277.
11. Neer RM, Arnaud CD, Zanchetta JR, *et al.* Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 2001; 344: 1434-1441.
12. Kurland ES, Cosman F, McMahon D, *et al.* Parathyroid hormone as a therapy for idiopathic osteoporosis in men: effects on bone mineral density and bone markers. *J Clin Endocrinol Metab* 2000; **85:** 3069-3076.
13. Orwoll ES, Scheele WH, Paul S, *et al.* The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 2003; **18:** 9-17.
14. Finkelstein JS, Hayes A, Hunzelman JL, *et al.* The effects of parathyroid hormone, alendronate, or both in men with osteoporosis. *N Engl J Med* 2003; **349:** 1216-1226.
15. Lane NE, Sanchez S, Modin GW, *et al.* Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis: results of a randomised controlled clinical trial. *J Clin Invest* 1998; **102:** 1627-1633.
16. Black DM, Greenspan SL, Ensrud KE, *et al.* The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* 2003; **349:** 1207-1215.
17. Cosman F, Nieves J, Woelfert L, *et al.* Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res* 2001; **16:** 925-931.
18. Lindsay R, Scheele WH, Clancy AD, Mitlak BH. Incident vertebral fractures during an 18-month observation period following discontinuation of LY333334 [recombinant human parathyroid hormone (1-34), rhPTH (1-34)] use in postmenopausal women with osteoporosis. *J Bone Miner Res* 2001; **16:** S162.
19. Vahle JL, Sato M, Long GG, *et al.* Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. *Toxicol Pathol* 2002; **30:** 312-321.
20. Tashjian AH jun., Chabner BA. Commentary on clinical safety of recombinant human parathyroid hormone 1-34 in the treatment of osteoporosis in men and postmenopausal women. *J Bone Miner Res* 2002; **17:** 1152-1161.
21. Rubin MR, Bilezikian JP. New anabolic therapies in osteoporosis. *Endocrinol Metab Clin North Am* 2003; **32:** 285-307.
22. Mitlak BH. Parathyroid hormone as a therapeutic agent. *Current Opinion in Pharmacology* 2002; **2:** 694-699.

Annexure A: Methodology

The National Osteoporosis Foundation (NOFSA) was approached by the manufacturer of teriparatide (Eli Lilly) to establish appropriate and cost-effective indications and treatment protocols for the use of this agent in the management of patients with osteoporosis.

A Working Group consisting of 6 senior Council Members of NOFSA was established. Following three meetings of the Working Group and the development of a draft position paper, a final document was electronically circulated to the entire Council of NOFSA. Amendments to this document were made where there was sufficient need in accordance with the comments received. The manufacturer was not involved in the establishment, content or funding of the position paper in any way. Once finalised, the position paper was sent for publication to the *South African Medical Journal*. The paper will also be available on the NOFSA web site (**www.osteoporosis.org.za**).

Annexure B: Patient assessment

Before initiating treatment with PTH (1-34)/teriparatide, a pro forma form containing the following clinical and laboratory data is to be completed so as to enable the Working Group to assess the application:

- History, physical examination and urinalysis (including risk factor assessment for osteoporosis and falls, fracture history, nature of and adherence to current therapy)
- BMD measurement of the spine and hip (DEXA)
- X-rays of the thoraco-lumbar spine (antero-posterior and lateral)
- Serum calcium, albumin, phosphate and total alkaline phosphatase
- Full blood count and sedimentation rate
- Serum protein electrophoresis
- Serum creatinine and uric acid
- Urine calcium and creatinine (24-hour urine collection)
- Serum gonadotrophins (LH, FSH), and testosterone (men) or oestradial (women in whom menopausal state is uncertain)
- Serum ALT, AST, GGT and bilirubin
- Serum osteocalcin and urine deoxypyridinoline (or equivalent biomarkers of bone turnover) to assess efficacy of antiresorptive therapy — unless the patient is not receiving any active treatment or has sustained a fracture in the preceding 3 months (known to increase biomarker levels).

For further information on the clinical, densitometric and laboratory assessment of patients with osteoporosis, the reader is referred to the SAMA Osteoporosis Clinical Guideline, *S Afr Med J* 2000, **90:** 905-944.

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