Position paper on the indications for the use of parathyroid hormone (PTH 1-34) in the treatment of osteoporosis

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Introduction
Parathyroid hormone (PTH) is a peptide hormone secreted by the parathyroid glands which, amongst many varied physiological effects, serves to maintain normal serum calcium levels. In fulfilling this function, the hormone interacts with its receptors in a number of tissues, including bone. One effect in bone is to stimulate pre-osteoblast formation and differentiation to mature functional osteoblasts and to prevent their apoptosis. Cytokines subsequently released by the osteoblasts then stimulate osteoclastic activity, bone breakdown and release of calcium into the circulation. Continued high level exposure of bone to PTH will result in eventual bone loss, but intermittent exposure will have an anabolic effect — fact which makes this peptide useful as a potent treatment for osteoporosis. Teriparatide is a 34 amino acid peptide which mimics the physiological effects of PTH and is registered in South Africa for the treatment of established osteoporosis with or without vertebral fractures in post menopausal women and in men.1 The intact human recombinant molecule PTH (1-84) is not available in South Africa and will not therefore be included in this discussion.

In 2004 the National Osteoporosis Foundation of South Africa (NOFSA) published a position paper on the use of PTH 1-34 in the treatment of osteoporosis. 2 This publication served to act as a guide for prescribing physicians on how best to decide on the use of an effective but expensive new drug in the setting of limited resources. Since this publication, more information has become available on the use of PTH 1-34, and an update is thus required.

Current indications include:
1. A low bone mineral density (BMD) and two or more prevalent fractures
2. Failed anti-resorptive therapy, after compliance with at least twelve months of treatment. Failure defined by:
   a. An incident fragility fracture
   b. Continued bone loss of ≥ 5% per annum as documented on two or more consecutive follow-up BMD measurements.

Methodology
Evidence supporting new guidelines for teriparatide use, were based on the following publications:
Firstly, a comprehensive review of the use of PTH for the treatment of osteoporosis, published in the Canadian Medical Association Journal.3,4 In this publication a systematic review of randomised controlled trials was undertaken and conclusions drawn on the efficacy and safety of PTH for fracture prevention. Data were collated from MEDLINE, EMBASE, HTA, Current Contents and the Cochrane Controlled Trials Registry.
Secondly, Endocrine reviews, under the auspices of the Multinational Endocrine Society reported a review of the evidence and suggested Guidelines for PTH use in March 2005.5
Thirdly, the United Kingdom based National Institute for Health and Clinical Excellence (NICE). The clinical effectiveness and cost effectiveness of technologies for the secondary prevention of osteoporotic fractures in postmenopausal women.6
Lastly, a review of parathyroid hormone treatment for osteoporosis published in Current Opinion in Endocrinology, Diabetes and Obesity in December 2008.7

Issues of importance include the following
1. The best anabolic response to teriparatide to increase BMD and improve microarchitecture, macroarchitecture and mass of bone, is in bisphosphonate naive patients and therefore it may have a role as first line treatment in selected patients.8
2. Patients with prior antiresorptive medication use, should be managed differently from drug naive patients considering starting teriparatide treatment. Evidence suggests that in patients currently taking alendronate or raloxifene, adding teriparatide rather than switching to teriparatide, may confer an improved BMD response with a trend towards fracture risk reduction.9,10 Ongoing trials will clarify outstanding fracture data.10
3. Teriparatide has not proven to be consistently more effective than bisphosphonate treatment for fracture prevention in post menopausal osteoporosis, as assessed in non-direct comparison trials via numbers needed to treat analyses.
4. Direct-comparison fracture data are available for 40 mcg of teriparatide (not the registered treatment dose in South Africa which is 20 mcg) and alendronate, demonstrating a significantly greater BMD increase and non-vertebral fracture reduction with use of the former versus the latter.\textsuperscript{11} Where 20 mcg of teriparatide was compared to alendronate, the clinical fracture rate after 18 months of treatment was the same in both groups.\textsuperscript{14} Long term data are not yet available.\textsuperscript{3,4,5}

5. Although DEXA scanning is used as a diagnostic tool for osteoporosis, patients with multiple fragility fractures and or multiple joint or bone surgical interventions may render the DEXA unreadable. These patients should be considered as having severe clinical osteoporosis.

6. PTH treatment is a limited therapeutic course, and in South Africa is prescribed for 18 months only, following which anti-resorptive treatment is recommended.

7. Glucocorticoid –induced osteoporosis should be regarded as a specific entity due to the drug-induced decrease in BMD as well as qualitative changes, causing osteoporosis. Therapeutic intervention thresholds which differ from those employed in primary osteoporosis are therefore appropriate.\textsuperscript{13,14,15}

All of the above recommendations are based on cost-effective management-principles in an attempt to minimize the cost of fracture prevention.

Due to the mechanism of action of teriparatide a full assessment of any patient initiating therapy should be undertaken to exclude any contraindications to the medication, and to rule out secondary causes of osteoporosis.

Contraindications to treatment include: known or suspected hypersensitivity to teriparatide, hypercalcemia or hypercalciuria, renal stones, gout, skeletal malignancy (primary or secondary), pregnancy, breastfeeding mothers, children with open epiphyses, bone disease other than osteoporosis, (such as primary hyperparathyroidism, Paget’s disease, osteomalacia) and any severe systemic organ dysfunction (especially chronic kidney or liver disease, ).

Once treatment has been initiated the patient should be made aware of known side effects- including occasional hypotension or tachycardia with the first few doses, nausea and leg cramps. Calcium and uric acid levels should also be monitored at 1, 6 and 12 months of treatment to ensure that the values remain within normal limits. Since calcium supplementation should be given together with Teriparatide the dose of the former may need adjustment.

**Conclusion**

Teriparatide is an anabolic drug with proven efficacy in the improvement of bone density and the reduction of both vertebral and non-vertebral fractures.\textsuperscript{16} but its cost, need for injection and the availability of cheaper drugs will limit its use. These NOFSA guidelines are an attempt to allow those patients at greatest fracture risk access to the medication they require.

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