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CLINICAL PRACTICE

New anabolic agents in the treatment of osteoporosis

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Osteoporosis is a common, serious disease characterised by a low bone mass and microarchitectural deterioration resulting in bone fragility and an increased risk of fracture. The mainstay of current therapies for osteoporosis is antiresorptive agents like calcium and vitamin D, oestrogen, selective oestrogen receptor modulators (SERMs), the bisphosphonates and calcitonin. These drugs inhibit osteoclast-mediated bone loss, reduce bone turnover (both resorption and formation), and modestly (less than 10%) increase bone mineral density (BMD). They reduce but do not eliminate fracture risk, and do not restore lost bone structure. Healthy, antiresorptive drugs should be employed to prevent osteoporosis, whereas osteo-anabolic agents, either alone or in combination with antiresorptives, should be used to treat established disease.

Anabolic agents directly stimulate bone formation by augmenting osteoblast proliferation and/or inhibition of osteoblast apoptosis. They have the potential to increase bone mass, restore skeletal microarchitecture 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 (GH) and insulinlike growth factor 1 (IGF-1). More recently, strontium, statins and parathyroid hormone (PTH) have been added to the list, with recombinant human PTH emerging as the most promising osteoanabolic agent to date.

Fluoride

Sodium fluoride markedly stimulates bone formation and increases axial BMD. However, randomised controlled trials employing high fluoride doses (up to 120 mg daily) have revealed no reduction in vertebral fracture incidence, despite an impressive increase in BMD.⁵ Moreover, adverse effects on the gastrointestinal tract and on cortical bone (a possible increase in hip fracture risk; lower extremity pain syndrome) were of concern. More recent studies, with a lower-dose enteric-coated formulation of fluoride, have been more encouraging.⁶ Combining fluoride and antiresorptive agents like oestrogen⁷ or bisphosphonates⁸ has also yielded more

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promising results. Fluoride, therefore, has the potential to be a useful drug in the treatment of osteoporosis, but further clinical trials are necessary before its routine use can be recommended.

GH and IGF-1

Both GH and IGF-1 promote osteoblast proliferation, and low levels of IGF-1 have been associated with an increased fracture risk.9 Results of prospective studies are disappointing, however.10 Changes in BMD have been modest, no fracture data are available, and treatment is associated with numerous adverse effects. Targeting IGF-1 to bone remains the biggest challenge before the treatment of osteoporosis with this agent can be realised.

Statins

Studies from Mundy's group have demonstrated that statins directly injected into the calvaria of mice result in increased bone formation, which is mediated by bone morphogenetic protein 2 (BMP-2), and prevented by mevalonate, a downstream metabolite of HMG coenzyme A reductase, which is the rate-limiting step in cholesterol biosynthesis. Statins are, however, almost entirely cleared via first-pass hepatic metabolism and do not localise to bone. Animal studies from our laboratory have confirmed that statins stimulate bone formation — bone resorption was also stimulated, however, resulting in a *decreased* BMD in rodents fed these lipid-lowering drugs. Finally, large clinical studies have failed to show a clear beneficial effect of statins on fracture risk. Further studies are therefore required to explore the osteoanabolic potential of these agents.

Strontium

Strontium ranelate appears from animal studies to have a dual action on skeletal tissue, stimulating osteoblastic bone formation and inhibiting osteoclastic bone resorption. Clinical trials have supported its efficacy and safety. In a large randomised placebo-controlled trial involving 1 649 postmenopausal women with at least one vertebral fracture, strontium ranelate was shown to decrease biochemical markers of bone resorption, increase markers of formation as well as BMD, and reduce the relative risk of new vertebral fractures by 41%.¹³ This agent holds much promise as a new anabolic agent in the management of osteoporosis.

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Parathyroid hormone (PTH)

Continuous exposure to high concentrations of PTH, as occurs in primary hyperparathyroidism, markedly stimulates osteoclastic bone resorption and decreases bone mass. Intermittent, low-dose PTH administration, on the other hand, causes rapid stimulation of bone formation which results in a marked increase in bone mass and strength, improvements in trabecular micro-architecture and cortical geometry, and a significant reduction in the risk of vertebral as well as nonvertebral fractures. Most clinical experience with PTH as an osteoanabolic agent has been obtained with the amino-terminal fragment of parathyroid hormone (PTH (1-34) or teriparatide), which will soon be available as a treatment for osteoporosis in South Africa. Clinical studies are also underway with intact human PTH (1-84), other fragments of PTH and of PTHrP, as well as calcilytics which stimulate the secretion of endogenous PTH.

The molecular sequence of events responsible for the anabolic skeletal effects of PTH remains to be elucidated. Daily subcutaneous injection of PTH (1-34) increases the osteoblast birth rate and prevents osteoblast apoptosis, thereby increasing the number of osteoblasts and the rate of new bone formation. 14,16 Biochemical markers of bone formation (e.g. bone alkaline phosphatase, BALP) start to increase within a few weeks of PTH administration and reach a maximum at 6 months, whereas resorption parameters (e.g. cross-linked Ntelopeptides, NTX) generally begin to rise after 2 - 4 months and peak at 12 months, thus providing an 'anabolic window' of some 6 - 9 months during which PTH is maximally anabolic. 18,19 PTH monotherapy (coupled with calcium and vitamin D supplementation) has been shown in numerous controlled trials to increase trabecular spine BMD by approximately 15% and total hip BMD by some 5%. 15-19 PTH in combination with antiresorptives like oestrogen increases lumbar BMD by nearly 30% and femoral BMD by 11%.20 While most studies have been performed in postmenopausal women with osteoporosis, PTH has also been shown to markedly increase BMD in models of low-turnover osteoporosis — notably in men with osteoporosis²¹ and in glucocorticoid-induced osteoporosis.²²

PTH not only increases BMD significantly more than current antiresorptive agents do^{18,19} but also improves bone size and microarchitectural deterioration. The latter includes an increase in trabecular number, decrease in trabecular spacing and major improvements in histological indices of trabecular connectivity, resulting in enhanced bone strength.²³⁻²⁴ Moreover, although potential PTH-induced loss of cortical bone was of concern earlier, recent studies have suggested similar anabolic effects and improved strength of this bone envelope.¹⁹

Do improvements in BMD and bone architecture following PTH administration result in a clinically significant reduction in fracture rates? Following a number of smaller studies suggesting that this was indeed the case, the results of a large

randomised, placebo-controlled trial involving 1 637 postmenopausal women were recently published. Compared with placebo, daily subcutaneous injection of human PTH (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%. A similar reduction in vertebral fracture rate was also documented recently in 437 men with osteoporosis. See 100 postmer 100 published.

Subcutaneous injection of PTH is generally well tolerated in a trial situation and compliance with treatment has been shown to be similar to that of patients taking oral bisphosphonates. This may very well change in real life — continued adherence to therapy will require patient education and motivation. 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 (urinary calcium excretion exceeding 7.5 mmol per day) and renal stone disease does not appear to increase. Ferum uric acid levels may increase by up to 20%, but clinical gout is not more prevalent in patients treated with PTH. Circulating antibodies to PTH developed in 3 - 8% of subjects, but does not have any discernible effect on outcomes.

Certain concerns about PTH still prevail. It is unclear whether PTH should ideally be prescribed as monotherapy or whether it should be combined with an antiresorptive drug. This is especially true following withdrawal of PTH treatment, after say 18 - 24 months. This may also be the case in subjects with predominantly cortical osteopenia. Certainly, ample daily calcium (1 000 mg) and vitamin D (400 - 1 200 IU) supplementation is mandatory. Of some concern too is the tumorigenic potential of PTH. Long-term studies with highdose PTH, administered to 6-week-old Fisher 344 rats, have demonstrated a dose-related increased risk of osteogenic sarcoma.26,27 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 have not been noted with increased frequency in patients with primary hyperparathyroidism or in any of the clinical trials performed in over 2 500 patients treated with PTH (1-34) for up to 3 years. 19,27 It is, therefore, reasonable to conclude that PTH is safe in human subjects, although ongoing safety data need to be collated.

As mentioned earlier, PTH (1-34) will soon be available as a treatment option for osteoporosis in South Africa. The local cost of this product will undoubtedly be high and serious ethical dilemmas will once again be posed with regard to the allocation of expensive resources. Clear indications for its use (e.g. antiresorptive therapy failue; very low prevalent BMD; high fracture risk score), close audit of its appropriate and cost-effective utilisation, and every effort to make this valuable drug

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available to all (including differential drug pricing in the private and public health sectors) will go a long way towards optimising the management of osteoporosis in this country.

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