Anabolic Agents: A New Chapter in the Management of Osteoporosis

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Abstract

Osteoporosis in postmenopausal women has until now been treated with antiresorptive agents, reducing the incidence of fragility fracture by approximately 50%. Clinical research has led to the development of new anabolic therapies capable of increasing the production of bone matrix by osteoblasts and reversing microarchitectural deterioration, resulting in major improvements in both bone quality and bone quantity. Teriparatide, a recombinant human parathyroid hormone consisting of the first 34 of 84 amino acids in human parathyroid hormone, has been shown to reduce significantly the risk of both vertebral and non-vertebral fractures in postmenopausal women. This agent was recently approved for use in Canada. Strontium ranelate is a new oral agent capable of uncoupling bone resorption from bone formation, which results in increases in bone formation with reductions in bone resorption. This agent has also been shown to reduce the risk of both vertebral and non-vertebral fracture while improving bone structure.

Anabolic therapies represent a major advance in the management of postmenopausal osteoporosis, and they may provide significant benefit to those patients with severe osteoporosis in whom antiresorptive therapy has proven insufficient. Anabolic therapies should complement the antiresorptive treatments currently available for use in women with postmenopausal osteoporosis.

Résumé

Jusqu'à présent, les femmes postménopausées présentant une ostéoporose ont été traitées au moyen d'inhibiteurs de la résorption osseuse, ce qui a entraîné une diminution de l'incidence des fractures de fragilisation d'environ 50 %. La recherche clinique a mené à la mise au point de nouveaux traitements anabolisants capables d'accroître la production de matrice osseuse par les ostéoblastes et de renverser la détérioration microarchitecturale, entraînant ainsi d'importantes améliorations tant en matière de quantité que de qualité osseuse. Il a été démontré que le tériparatide, hormone parathyroïdienne humaine recombinée qui est formée des 34 premiers acides aminés des 84 que contient l'hormone parathyroïdienne humaine, entraînait une nette réduction du risque de fractures (tant vertébrales que non vertébrales) chez les femmes postménopausées. Au Canada, l'utilisation de cet agent a récemment été approuvée. Le ranélate de strontium est un nouvel agent à administration orale capable de découpler la résorption de la formation osseuse, ce qui entraîne la hausse de cette dernière et la baisse de la résorption osseuse. Il a également été démontré que cet agent entraînait une réduction du risque de fractures (tant vertébrales que non vertébrales), tout en améliorant la structure osseuse.

Les traitements anabolisants constituent une percée importante dans le domaine de la prise en charge de l'ostéoporose postménopausique. De plus, il est possible qu'ils offrent un net avantage aux patientes présentant une ostéoporose grave chez lesquelles le recours aux inhibiteurs de la résorption osseuse s'avère insuffisant. Les traitements anabolisants devraient compléter les inhibiteurs de la résorption osseuse actuellement offerts aux femmes qui connaissent une ostéoporose postménopausique.

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INTRODUCTION

Osteoporosis is a condition characterized by a decrease in bone mass associated with microarchitectural deterioration of bone, which results in increased bone fragility and an increased risk of fracture.[1,2] Until recently, all approved treatments proven to reduce the risk of vertebral and non-vertebral fractures were antiresorptive agents. For postmenopausal women, these included the bisphosphonates, raloxifene, calcitonin, and hormone replacement therapy. Antiresorptive agents decrease bone turnover by decreasing osteoclast activity. The biochemical markers of bone turnover decrease, and bone microarchitecture is preserved, which is associated with reductions in fracture incidence.[3] Antiresorptive agents reduce the frequency of activation of new remodelling units, resulting in greater time available for mineralization of bone.[4] The increases in bone density reflect increases in secondary mineralization. Antiresorptive agents have no anabolic skeletal effects and are unable to repair damaged microarchitecture. Many patients with severe osteoporosis remain at increased risk for fracture.

In contrast, anabolic agents increase osteoblast function. An increase in the production of bone matrix by osteoblasts

can occur, as well as an increase in the actual number of osteoblasts. Several anabolic agents have been evaluated in the management of osteoporosis. The purpose of this review is to summarize the known skeletal effects of these agents, specifically, of fluoride, growth hormone, the statins, parathyroid hormone, and strontium ranelate.

FLUORIDE

Fluoride was the first anabolic agent evaluated for treating postmenopausal women.[5] Fluoride stimulates osteoblast activity. With low doses, bone mass increases and the risk of vertebral fractures decreases in patients with postmenopausal osteoporosis.[6,7] In high doses, a reduction in vertebral fractures is not seen,[8] but increased numbers of non-vertebral fractures in sodium fluoride-treated patients have been reported,[9] raising concerns about impaired bone quality and negative effects on bone strength with sodium fluoride therapy. In lower doses, monofluorophosphate therapy has been shown to reduce the incidence of vertebral fractures, although these studies are based on small numbers of patients.[10] Because of conflicting data on fracture incidence with fluoride therapy, this treatment option is no longer recommended for the management of osteoporosis. Adverse effects of fluoride have included gastrointestinal symptoms and lower extremity pain syndrome.[8]

GROWTH HORMONE

Growth hormone (GH) and insulin-like growth factor-1 (IGF-1), a by-product of GH release, play key roles in the acquisition of peak bone mass and in the maintenance of bone mineral density (BMD). Insulin-like growth factor-1 stimulates osteoblast differentiation, and IGF-1 deficiency has been associated with increased fracture risk.[11,12] It is released by the bone matrix during bone resorption. Both recombinant human growth hormone and IGF-1 have anabolic skeletal effects and, by increasing bone density, may decrease fracture risk. Patients with acromegaly have been evaluated regarding fracture risk, which appears to be lower in this population.[13] Treatment with growth hormone has been proposed as an option for individuals with osteoporosis, even in the absence of growth hormone deficiency.[14] Growth hormone increases bone mineral content in the postmenopausal osteoporotic population, and individuals treated with growth hormone appear to have a lower fracture risk.[14] However, well-designed longitudinal studies are needed to confirm these effects of growth hormone on fracture risk.

Use of recombinant human growth hormone (RHGH) has been limited by the high incidence of side effects, including weight gain, carpal tunnel syndrome, glucose intolerance, and edema. This has limited its utilization in the elderly in particular. Moreover, in elderly individuals with osteoporosis, GH may not have an appreciable effect on bone density.[15]

Combination therapy with RHGH and calcitonin has been evaluated by Holloway and colleagues. Their two-year randomized trial demonstrated a modest 2.7% increase in spinal BMD with combination therapy, but the change at the hip sites was not significantly different from that achieved using calcitonin alone.[15] However, significant side effects were attributed to RHGH. The gains in BMD were less marked than those seen with estrogen or the aminobisphosphonates, and they were associated with a higher incidence of adverse experiences.[15] GH releasing analogues appear to be better tolerated and may become promising agents in the future.[16] IGF-1 may be more useful than GH in treating osteoporosis, as it has a more direct skeletal effect. In addition, IGF-1 may be less likely than RHGH to cause such GH-related side effects as carpal tunnel syndrome[17,18] and diabetes mellitus.[19,20] Unfortunately, published clinical research with IGF-1 is limited. Combinations of RHGH or IGF-1 with antiresorptive therapies warrant further investigation.

STATINS

In vitro studies of lovastatin or simvastatin injected into mouse skulls have demonstrated the anabolic effects of statins. Use of statins in these studies was associated with increased bone formation.[21] Statins are HMG-CoA reductase inhibitors. They appear to produce their anabolic effect by increasing the production of bone morphogenetic protein-2, thereby increasing bone formation.[22,23] Animal studies have shown an increase in bone mass with local or systemic administration of statins.[24–26] However, studies evaluating the effects of long-term statin therapy on osteoporotic fracture have not been conclusive regarding beneficial skeletal effects and fracture reduction.[27–31] In the Women's Health Initiative trial of combined estrogen-progestin therapy in postmenopausal women, the age-adjusted rates of fracture in statin users and non-users were not different.[32] In addition, there was no difference in bone density between statin users and non-users in these postmenopausal women after adjusting for age, body mass index, ethnicity, and other factors. It is possible that the doses used in lipid lowering are insufficient to produce detectable anabolic skeletal effects. In the future, more potent agents may provide evidence of more significant skeletal effects.

In summary, current evidence does not support the use of statins in the prevention or treatment of osteoporosis.

PARATHYROID HORMONE

Teriparatide (TPD) is a recombinant fragment (amino acid residues 1–34) of endogenous human parathyroid hormone (PTH), itself an 84-amino acid molecule. TPD was approved for use in Canada in June 2004 for the treatment of osteoporosis in postmenopausal women and to increase bone density in men. The approved duration of treatment is 18 months. It is recognized that continuously high PTH levels, as seen in individuals with primary hyperparathyroidism, are associated with decreases in bone density; however, intermittent PTH administration appears to stimulate bone formation and to increase BMD.[33,34] Clinically, intermittently administered TPD results in stimulation of osteoblastic effects[35,36]; given continuously in the same daily doses, it results in enhanced osteoclast formation and activity and increased bone resorption.[36]

In daily doses of 20 μg administered subcutaneously, TPD concentrations in the plasma peak 30 minutes after injection and are undetectable in three to four hours.[37]

TPD has multiple effects on bone cells, including the stimulation of osteoblastic and osteoclastic activity; however, the net effect is in favour of bone formation. TPD stimulates the differentiation of bone lining cells and preosteoblasts to osteoblasts, resulting in a net increase in the number and activity of bone forming osteoblasts.[38]

In a randomized controlled trial (RCT) of postmenopausal women with fragility fractures, TPD in doses of 20 μg daily over 12 months increased lumbar spine BMD by 9%.[39] Femoral and whole body BMD also increased. In TPD-treated women, the risk for vertebral fractures was reduced by 65%, and for non-vertebral fractures by 53%.[39] Bone biopsies of patients treated with TPD have demonstrated an increase in the thickness and number of trabeculae, as well as increases in the density of trabecular connections, cortical thickness, and bone size, thereby producing restoration of the microarchitecture of the bone with major improvements in bone strength.[40]

TPD has been evaluated in combination with bisphosphonates, as well as in combination with postmenopausal hormone therapy (HT). Combining HT and TPD results in larger increases in lumbar spine and hip bone density than use of HT alone.[41,42] A greater effect on vertebral fracture risk may be seen with combinations of HT and TPD than with HT alone.[42] In one study involving postmenopausal women with osteoporosis,[43] the concurrent use of alendronate and PTH blunted the anabolic effects of TPD. Long-term studies of fracture risk are required to determine whether bisphosphonates can indeed be used concurrently with TPD.

Treatment with TPD after bisphosphonate therapy has also resulted in relative blunting of the usual anabolic response to TPD. Similar blunting has not been reported following estrogen or raloxifene therapy.[44] Bone biopsies have shown that TPD significantly increases cortical bone thickness and improves bone architecture and connectivity.[45] TPD is the first agent to have produced a demonstrable improvement in bone microarchitecture. TPD increases periosteal bone formation as well as bone size, thereby significantly improving microarchitecture and bone strength.[46]

TPD is well tolerated. Minor side effects (nausea and headache) have been reported by postmenopausal women treated with TPD. Transient mild hypercalcemia also may occur.[38] Osteosarcoma, a theoretical risk, has not been reported in humans treated with TPD. Previously, clinical studies were discontinued because of an increased risk of osteosarcoma identified in rats receiving high-dose TPD throughout life.[47] However, the osteosarcomas seen in the rat studies were dose-dependent and were observed when doses greater than 5 μg/kg/day were administered continuously from birth to the time of sacrifice. The dose approved for use in humans is 20 μg day or approximately 0.28 μg/kg/day for a limited period of 18 months. When TPD has been administered in these doses and for these limited time periods, no cases of osteosarcoma have been reported. Osteosarcoma has also not been reported in other animal studies, including those involving monkeys. It is noteworthy that osteosarcoma does not occur with an increased frequency in individuals with primary hyperparathyroidism.

TPD has been documented to improve bone strength and to reduce the risk of both vertebral and non-vertebral fractures. The duration of therapy with TPD is limited to 18 months. Following TPD therapy, the gains in bone density and bone quality are maintained by antiresorptive agents like bisphosphonates or raloxifene. TPD is a welcome addition to the other therapies currently available for postmenopausal osteoporosis.

STRONTIUM RANELATE

This compound consists of two atoms of strontium and organic ranelic acid. Strontium ranelate (SR) is a compound that can be incorporated into bone at the same rate as calcium and that can accumulate in the skeleton because of its chemical and physical similarities to calcium.[48] It is present in soil and water and is naturally present in small amounts in blood, bones, and soft tissue. It is actively absorbed in the bowel and its absorption is vitamin D-dependent. Its absorption decreases in older patients and in the presence of high dietary calcium intake. SR, as a replacement for calcium, is incorporated on the crystal surface of the bone.

Crystals containing strontium are more stable.[49] The skeletal effects of SR arise from its action on bone cells: it stimulates preosteoblast replication and increases matrix synthesis. Furthermore, SR inhibits osteoclast differentiation and activity, decreasing bone resorption. It also stabilizes the hydroxyapatite crystal and may indirectly inhibit the resorption of calcified matrix.[49,50]

SR has been shown to stimulate bone formation and inhibit bone resorption in rats.[51] In ovariectomized rats, SR has been shown to prevent bone loss by decreasing bone resorption and increasing bone formation.[51] Because strontium has a higher atomic number than calcium, when it is present in bone it results in an over-estimation of BMD. In clinical trials evaluating strontium, increases in BMD have been seen that persist even after adjusting BMD for the presence of strontium. RTCs evaluating SR therapy in postmenopausal women, for both prevention and treatment of postmenopausal osteoporosis, have been completed. In one phase 2 osteoporosis prevention study, 160 early postmenopausal women were randomized to receive placebo or several different doses of SR.[52,53] Treatment over two years resulted in an increase in lumbar spine bone density compared with placebo. In another phase 2 osteoporosis treatment study, 353 osteoporotic postmenopausal women were randomized to receive SR in varying doses or placebo.[54] On 2 g of SR per day, there was an increase in bone density in the SR group compared with placebo and a significant reduction in the number of patients experiencing new vertebral fractures in the second year of treatment.[54] In both studies, an increase in serum levels of biomarkers for bone formation was noted, including increases in bone alkaline phosphatase. Markers of bone resorption, specifically urinary excretion of N-telopeptide, were lower in the strontium group than in the placebo group.

The 2 g per day dose of SR is considered to offer the best combination of efficacy and safety[54] in treating postmenopausal osteoporosis. The results of a phase 3 clinical trial recently were published, in which 2 g daily SR was compared with placebo over three years in 1649 postmenopausal women with osteoporosis.[55] A 49% reduction in new vertebral fractures was seen at year one in the SR versus placebo group. A significant effect on non-vertebral fractures was not found. The treatment was very well tolerated, with a safety profile comparable to placebo. No negative effects on bone mineralization were noted.[55] Another five-year trial comparing the effectiveness of SR with placebo on non-vertebral fractures in postmenopausal women recently published the three years of treatment main statistical analysis. A significant reduction in non-vertebral fractures (16% reduction, $P = 0.04$) has been reported.[56] Those in the high-risk subgroup (women ≥ 74 years of age and a femoral neck BMD T-score ≤ 3) have demonstrated an even greater reduction in hip fracture risk (36%, $P = 0.046$).

In summary, SR has been shown to be effective in reducing the risk of vertebral and non-vertebral fractures, especially hip fractures, in postmenopausal women at high risk for fracture. The tolerability profile was similar to placebo with side effects being limited to nausea and diarrhea during the first few months of therapy.[53] SR is a most promising agent for treatment of postmenopausal osteoporosis.

CONCLUSIONS

We are entering a new era in the management of osteoporosis. With the availability of anabolic agents to complement antiresorptive therapies, our ability to manage osteoporosis effectively will be greatly enhanced. The new anabolic agent TPD is well tolerated and effective in reducing fractures and restoring bone microarchitecture. Dual acting SR is capable of decreasing bone resorption and also increasing bone formation. Current experience with combination therapy is very limited and such combinations need to be evaluated carefully. Antiresorptive agents and anabolic agents may be of great value as complementary agents, best used sequentially, allowing improvements in bone microarchitecture to be maintained with a significant reduction in fracture risk. Strategies for combination therapy may allow us to move closer to a cure for this common condition.

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