New insights into treatment of osteoporosis in postmenopausal women

Piet Geusens¹,²

ABSTRACT

For the prevention of fractures, antiresorptive drugs (bisphosphonates and denosumab) that decrease high bone resorption and, secondarily, also bone formation, are the mainstream of therapy. Osteoanabolic drugs, such as teriparatide, increase bone formation more than bone resorption, and are used in severe osteoporosis, including patients treated with antiresorptive drugs who still lose bone and have recurrent fractures. New potential drugs for fracture prevention that uncouple bone resorption from bone formation include odanacatib, a specific inhibitor of cathepsin-K, the enzyme that degrades bone collagen type I, that inhibits bone resorption and only temporarily bone formation, and monoclonal antibodies against sclerostin (romosozumab, blosozumab), that stimulate bone formation and decrease bone resorption.

The aetiology of fractures is multifactorial, including factors that increase the risk of bone fragility and the risk of falls.¹ In terms of bone fragility, the final pathway is the degree and balance of bone turnover and the quality of the remodelled bone.² In the majority of postmenopausal women at risk for fractures, bone remodelling, expressed as activation frequency of bone remodelling units, is increased.³ Therefore, antiresorptive therapy that decreases high bone turnover has been developed as a major approach for fracture prevention. In patients with severe osteoporosis and in patients with low remodelling such as in glucocorticoid osteoporosis, osteoanabolic treatment should be considered (figure 1). Nevertheless, treatment of osteoporosis is not only drug treatment: sufficient calcium and vitamin D intake, a healthy lifestyle and prevention of falls are also important. We review new insights in antiresorptive and osteoanabolic drug therapy for fracture prevention.

ANTIRESORPTIVE THERAPY

Estrogens have a multitude of actions on bone, both directly on bone cells, and indirectly by their influence on bone marrow and immune cells.⁴ Because of side effects of combined estrogen plus progestin (E+P), the use of E+P has dropped significantly in the USA.⁵ As a result, Roth et al⁶ estimated that the 10-year incidence in the USA of cardiovascular diseases in women (76 000 fewer cases) and breast cancer (126 000 fewer cases) would have dropped significantly, but the 10-year incidence of hip, vertebral and other osteoporotic fractures would increase (263 000 more fractures in women). This resulted in an estimated net economic return of US$35 billion. However, other factors could play a role in these estimations, such as better lifestyle, but still a net economic return of US$25 billion was estimated when only 50% of the changes in side effects were attributed to the drop rate of E+P. Selective estrogen receptor modulators (SERMs) have been developed as an alternative for estrogens. Several SERMs have been shown

Key messages

What is already known?

▸ Anti-resorptive drugs are the mainstream treatment in the prevention of fractures in high-risk patients.

▸ Teriparatide is an osteo-anabolic drug that increases bone formation more than bone resorption, and is used in the treatment of severe osteoporosis.

What might this study add?

▸ New potential drugs for fracture prevention include odanacatib, a specific inhibitor of cathepsin-K that only temporarily suppresses bone formation, and monoclonal antibodies against sclerostin, that stimulate bone formation and decreases bone resorption.

How might this impact on clinical practice?

▸ The availability of a wide range of drugs to prevent fractures, with different effects on bone resorption and formation, further widens perspectives for individualized and targeted fracture prevention in high-risk patients.
to decrease the risk of vertebral fractures. Of the SERMs studied for fracture prevention, raloxifen has also been demonstrated to reduce the risk of breast cancer. However, SERMs also have adverse effects, such as thromboembolic disorders.

Currently, the most prescribed antiresorptive drugs are bisphosphonates (BPs) and denosumab. Nitrogen-containing BPs bind to bone surfaces and inhibit the mevalonate pathway in osteoclasts, which results in apoptosis of the osteoclasts, an inhibition that can persist over a long time after stopping long-acting BPs such as zoledronate and alendronate. Denosumab is a fully human monoclonal antibody that specifically binds receptor activator of the nuclear factor kappa-B ligand (RANKL) and so inhibits differentiation and activation of osteoclasts during 6 months, an inhibition that resolves within 1 year after stopping. Alendronate, riseredronate, zoleodronate and denosumab have a broad spectrum of fracture prevention in patients with osteoporosis and/or a prevalent vertebral fracture, decreasing the risk of vertebral fractures by more than 50%, the risk of non-vertebral fractures by 20–25% and of hip fractures by 40–50%. Antiresorptive drugs suppress the birth of new remodelling units, with fewer and shallower resorption cavities, and maintain bone structure with more complete mineralisation. Long-term studies with alendronate (5+5 years) and zoledronate (3+3 years) indicate a favourable effect on vertebral fractures. For alendronate, this was found for clinical vertebral fractures in a post hoc analysis in patients with persisting osteoporosis in the femoral neck, and a prevalent vertebral fracture after an initial 5-year treatment. For zoledronate, this was found for morphometric vertebral fractures after an initial 5-year treatment in patients still at high risk of fracture, such as having a vertebral fracture, but not after longer treatment. During long-term treatment with denosumab over 8 years, the fracture risk for vertebral and non-vertebral fractures remained low, at the levels achieved during the initial 3-year FREEDOM study. Compared with weekly oral alendronate, patients preferred denosumab over alendronate, with significantly better compliance for denosumab in a crossover study during 2 years.

Specific side effects with oral BPs include gastrointestinal (GI) problems and flu-like symptoms after the first infusion of zoledronate. BPs, but not denosumab, are contraindicated in patients with impaired renal function. The rarely occurring cellulitis/erysipelas (<0.5%) with denosumab in the FREEDOM study was not found during long-term follow-up studies. An increased risk of atypical femoral fractures (AFF) and osteonecrosis of the jaw (ONJ) has been reported with antiresorptive drugs, especially with high doses of intravenous BPs and of denosumab as used in patients with cancer. In osteoporosis treatment, the risk for ONJ is estimated to be between 1 in 1000 and 1 in 263 000 patient years. The risk of ONJ is multifactorial, including glucocorticoid use, poor oral hygiene, infection, dental extraction and smoking. The risk of AFF was 1.8/10 000 patients/year for up to 2 years of treatment, and 8.4/10 000 patients/year with use of more than 2 years. The cause of AFF is unclear. An association of AFF with hypocalcaemia due to latent hypoparathyroidism, age, obesity, early menopause, bone mineral density (BMD) and the degree of bowing of the femur has been postulated. Hypocalcaemia is a potential side effect of zoledronate and denosumab, especially in high-risk patients (such as gastric bypass, malabsorption, vitamin D deficiency, severe renal insufficiency, cancer with bone metastases).
and can last for 1–2 months.\textsuperscript{23,24} To avoid serious hypo-
calcaemia, pretreatment calcium and vitamin D status should be assessed and corrected if appropriate.

\textit{Odanacatib} is a specific inhibitor of cathepsin-K, the
enzyme that is secreted by osteoclasts and that degrades
type I collagen. Odanacatib increases BMD in the
spine and hip, an effect that is immediately reversible
after stopping the drug.\textsuperscript{25} As expected, bone markers of
bone resorption remained suppressed during treatment,
but interestingly there was only a temporary suppression of
bone formation, by contrast with other antiresorptive
drugs, indicating uncoupling of bone resorption and
bone formation over time with odanacatib.\textsuperscript{26} Preliminary
data, presented at the American Society of Bone and
Mineral Research (ASBMR) in 2014, indicate a signifi-
cant reduction of the risk of vertebral, non-vertebral and
hip fractures.\textsuperscript{27} A significantly increased risk, but with
low incidence, of morphea-like skin lesions (0.1\%) and
AFF (0.1\%) was reported. No other significant safety
issues are reported up until now in the available prelimi-
nary reports.\textsuperscript{28} For more stringent interpretation and
conclusions, a peer-reviewed publication of the results of
the trial is awaited.

**OSTEOANABOLIC THERAPY**

\textit{Mechanical signals} can act such as anabolic agents in
bone.\textsuperscript{29} Large, intense challenges to the skeleton, and
brief exposure to mechanical signals of high frequency and
extremely low intensity have been shown to provide a
significant anabolic stimulus to bone. Physical activity
has a positive effect on building the peak bone mass
and density.\textsuperscript{30} Physical activity has a direct effect on
osteoblast and osteocyte activity, but could also bias mes-
enchymal stem cell differentiation towards osteoblasto-
genesis and away from adipogenesis.\textsuperscript{29,30} This indicates
that physical activity, at least during growth, targets the
bone marrow stem cell pool and might, therefore, be
considered a novel, drug-free osteoanabolic approach.

\textit{Teriparatide}, a recombinant human PTH 1–34 fragment
[\textit{rhPTH}(1–34)] is currently the only available osteoana-
bolic drug. In patients with severe osteoporosis, daily
subcutaneous injections of teriparatide during
18 months decreases the risk of vertebral fractures by
65\% and the risk of non-vertebral fractures by 53\%.\textsuperscript{31,32}
By contrast with antiresorptive therapy, \textit{rhPTH}(1–34)
increases bone formation by inhibiting sclerostin pro-
duction by osteocytes and increases bone resorption by
stimulation of RANKL production by osteoblasts and
osteocytes. As teriparatide increases bone formation
more than bone resorption, this results in the so-called
anabolic window, during which the actions of teripara-
tide are believed to be maximally anabolic.\textsuperscript{33,34} In trabecular
bone, teriparatide increases BMD and trabecular thickness.\textsuperscript{35}
In cortical bone, it increases endosteal bone remodelling and periosteal bone forma-
tion.\textsuperscript{36} Taken together, these findings indicate that teri-
paratide has an effect on both bone remodelling and
modelling.\textsuperscript{34} After 18–24 months of treatment, the newly
formed lowly mineralised bone is quickly lost and there-
fore needs to be preserved and further mineralised with
subsequent use of antiresorptive drugs.\textsuperscript{37}

Teriparatide has been studied with other time intervals
than daily injections, and with other applications (trans-
dermal needle patch, oral, inhaled). Using hip structural
analysis based on dual-energy X-ray absorptiometry,
one weekly teriparatide during 72 weeks showed signifi-
cantly higher BMD, average cortical thickness, bone
cross-sectional area, and section modulus, and lower
buckling ratio at both the femoral neck and the intertro-
chanteric regions compared with placebo.\textsuperscript{38} Once
weekly injections of teriparatide reduced the risk of new vertebral fracture by 80\% after 72 weeks of treatment.\textsuperscript{39}

Side effects have been recently reviewed.\textsuperscript{40}
Osteosarcoma was found in rats treated for 2 years with
teriparatide. However, a report on 549 patients with
osteosarcoma in the USA did not reveal any cases of teri-
paratide exposure prior to the diagnosis of osteosar-
coma.\textsuperscript{41} Mild hypercalcaemia 4–6 h after injection is
rare (11\%), with low recurrence rate. GI symptoms and
dizziness are also reported.

In the conquest of understanding mechanisms of
bone formation, the discovery of the Wnt signalling
pathway has opened the way to new osteoanabolic treat-
ments.\textsuperscript{34} Sclerostin and dickkopf inhibit bone formation.
They protect bone from excessive bone formation, as
has been shown for sclerostin in van Buchem’s disease,
which is characterised by excessive bone formation in
the skull and mandibula.\textsuperscript{34} Sclerostin protects against
excessive bone formation.

Studies with monoclonal antiscleostin antibodies in
animals have shown that these antibodies stimulate bone
formation directly, through bone modelling, thus at
least, in part, independent of bone remodelling and
activation frequency.\textsuperscript{34} Additionally, these antibodies stim-
ulated the production of osteoprotegerin (OPG),
resulting in a decrease in bone resorption, leading to
uncoupling of bone formation and bone resorption,
potentially resulting in an even greater anabolic window
than teriparatide.\textsuperscript{34}

Subcutaneous injections of the antiscleostin antibody
\textit{romosozumab} have been studied in phase I and II
trials.\textsuperscript{42,43} In postmenopausal women with low bone
mass, a monthly dose of 210 mg romosozumab during
12 months was associated with a significantly increased
BMD (+11.3\% in the spine, +4.1\% in the total hip,
+3.7\% in the femoral neck), which was significantly
higher than with weekly alendronate or daily teripara-
tide. There was a transient increase in markers of bone
formation during the first 3 months together with an
initial 2-month decrease in markers of bone resorption,
which was to a lesser degree sustained during
12 months. Except for mild, generally non-recurring
injection-site reactions with romosozumab, adverse
events were similar among groups. Subcutaneous injec-
tions of the antiscleostin antibody \textit{blosozumab} have been
studied in phase I and II trials.\textsuperscript{44, 45} Dose-dependent responses were observed in sclerostin, N-terminal propeptide of procollagen type 1, bone-specific alkaline phosphatase, osteocalcin, C-terminal fragment of type 1 collagen, and BMD after single and multiple (up to 5) administrations of blosozumab. After 1 year in the highest dose group, BMD increases from baseline reached 17.7% at the spine, and 6.2% at the total hip. Blosozumab was well tolerated with no safety concerns identified after single or multiple administrations up to 750 mg. Phase III fracture prevention trials with anti-sclerostin antibodies are ongoing.

Combination therapy of osteoanabolic with antiresorptives in clinical trials showed effects on BMD that depended on the timing (before, during or after antiresorptive treatment), the drug studied and the site of measurement.\textsuperscript{46–50} The most consistent effect of combination therapy of antiresorptives and teriparatide is found in hip BMD, where combination therapy was superior to teriparatide alone, and in spine BMD, where combination with denosumab was superior to teriparatide alone.\textsuperscript{46–50} None of the studies were powered to study an effect on fracture risk.\textsuperscript{50}

Sequential therapy of antiresorptives and osteoanabolic treatment has been documented by its effect on BMD.\textsuperscript{49} In patients treated with BPs who still develop fractures or still lose BMD, switching to teriparatide is advocated.\textsuperscript{49} However, continuing antiresorptive treatment when starting teriparatide resulted in a better response of BMD in the hip.\textsuperscript{51} As aforementioned, antiresorptive treatment is indicated after stopping teriparatide in order to preserve the increased bone architecture and to increase its mineralisation.

In conclusion, the availability of antiresorptive and osteoanabolic drugs has enlarged our ability to maximise fracture prevention (figure 1). The arrival of odanacatib and anti-sclerostin antibodies will, hopefully, allow further individualising fracture prevention according to the fracture risk of the individual patient at risk. What will further be needed are therapies that decrease the risk of non-vertebral fractures to a higher degree than with the available antiresorptive drugs, which decrease the risk of non-vertebral fractures by 25%.\textsuperscript{52} The preliminary results of odanacatib indicate similar non-vertebral fracture reductions as antiresorptive drugs. Teriparatide showed a reduction of 50% of non-vertebral fractures, indicating that osteoanabolic drugs could have the promise of further reducing the risk of non-vertebral fractures. Direct comparison trials with fracture prevention as endpoint between teriparatide and BPs and between romosozumab and BPs are ongoing, and could give an answer to this question.\textsuperscript{53}

Competing interests None declared.

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