

## REVIEW

New insights into treatment of  
osteoporosis in postmenopausal womenPiet Geusens<sup>1,2</sup>

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## 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.<sup>1</sup> In terms of bone fragility, the final pathway is the degree and balance of bone turnover and the quality of the remodelled bone.<sup>2</sup> In the majority of postmenopausal women at risk for fractures, bone remodelling, expressed as activation frequency of bone remodelling units, is increased.<sup>3</sup> 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

## 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.

indirectly by their influence on bone marrow and immune cells.<sup>4</sup> Because of side effects of combined estrogen plus progestin (E+P), the use of E+P has dropped significantly in the USA.<sup>5</sup> As a result, Roth *et al*<sup>5</sup> 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



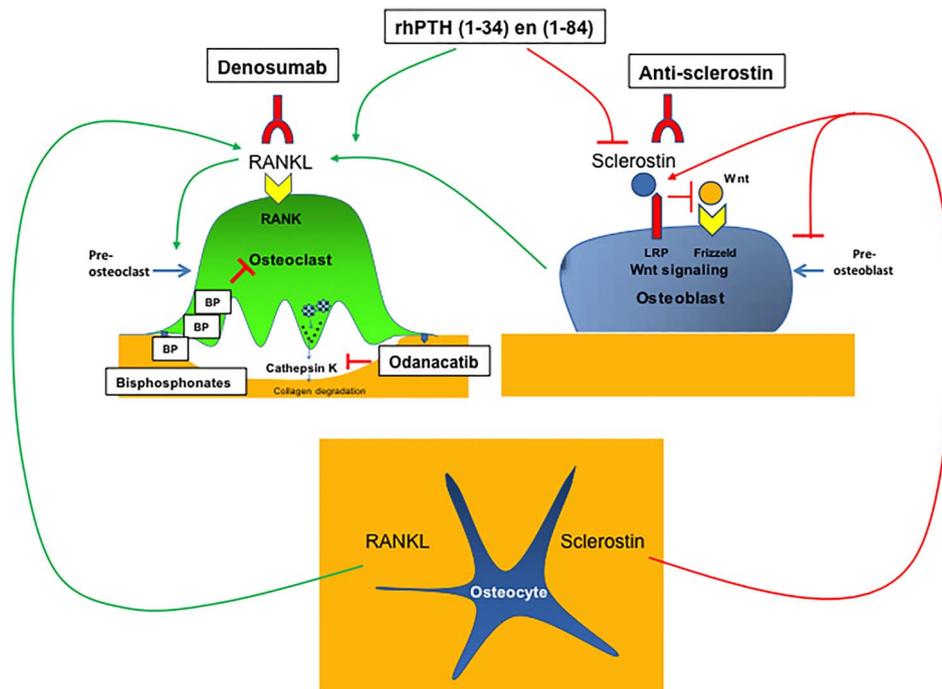
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**Figure 1** Schematic representation of the effect of antiresorptive and osteoanabolic drugs on bone.



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.<sup>6</sup> However, SERMs also have adverse effects, such as thromboembolic disorders.<sup>7 8</sup>

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.<sup>9</sup> 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.<sup>10</sup> Alendronate, risedronate, zoledronate 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%.<sup>11</sup> 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.<sup>12 13</sup> 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.<sup>12</sup> For zoledronate, this was found for morphometric vertebral fractures after an initial 3-year treatment in patients still at high risk of fracture, such as having a

vertebral fracture, but not after longer treatment.<sup>13 14</sup> 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.<sup>15</sup> Compared with weekly oral alendronate, patients preferred denosumab over alendronate, with significantly better compliance for denosumab in a crossover study during 2 years.<sup>16</sup>

Specific side effects with oral BPs include gastrointestinal (GI) problems and flu-like symptoms after the first infusion of zoledronate.<sup>17 18</sup> BPs, but not denosumab, are contraindicated in patients with impaired renal function.<sup>19</sup> 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.<sup>20 21</sup> 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.<sup>17</sup> 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.<sup>22</sup> 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.<sup>23 24</sup> To avoid serious hypocalcaemia, pretreatment calcium and vitamin D status should be assessed and corrected if appropriate.

*Odanacatib* is a specific inhibitor of cathepsin-K, the enzyme that is secreted by osteoclasts and that degrades bone type I collagen. *Odanacatib* increases BMD in the spine and hip, an effect that is immediately reversible after stopping the drug.<sup>25</sup> 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*.<sup>26</sup> Preliminary data, presented at the American Society of Bone and Mineral Research (ASBMR) in 2014, indicate a significant reduction of the risk of vertebral, non-vertebral and hip fractures.<sup>27</sup> 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 preliminary reports.<sup>28</sup> For more stringent interpretation and conclusions, a peer-reviewed publication of the results of the trial is awaited.

## OSTEOANABOLIC THERAPY

*Mechanical signals* can act such as anabolic agents in bone.<sup>29</sup> 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.<sup>30</sup> Physical activity has a direct effect on osteoblast and osteocyte activity, but could also bias mesenchymal stem cell differentiation towards osteoblastogenesis and away from adipogenesis.<sup>29 30</sup> 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.

*Teriparatide*, a recombinant human PTH 1–34 fragment [rhPTH(1–34)] is currently the only available osteoanabolic 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%.<sup>31 32</sup> By contrast with antiresorptive therapy, rhPTH(1–34) increases bone formation by inhibiting sclerostin production 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 teriparatide are believed to be maximally anabolic.<sup>33 34</sup> In trabecular bone, teriparatide increases BMD and trabecular thickness.<sup>35</sup> In cortical bone, it increases endosteal bone remodelling and periosteal bone formation.<sup>36</sup> Taken together, these findings indicate that teriparatide has an effect on both bone remodelling and

modelling.<sup>34</sup> After 18–24 months of treatment, the newly formed lowly mineralised bone is quickly lost and therefore needs to be preserved and further mineralised with subsequent use of antiresorptive drugs.<sup>37</sup>

Teriparatide has been studied with other time intervals than daily injections, and with other applications (transdermal needle patch, oral, inhaled). Using hip structural analysis based on dual-energy X-ray absorptiometry, once weekly teriparatide during 72 weeks showed significantly higher BMD, average cortical thickness, bone cross-sectional area, and section modulus, and lower buckling ratio at both the femoral neck and the intertrochanteric regions compared with placebo.<sup>38</sup> Once weekly injections of teriparatide reduced the risk of new vertebral fracture by 80% after 72 weeks of treatment.<sup>39</sup>

Side effects have been recently reviewed.<sup>40</sup> 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 teriparatide exposure prior to the diagnosis of osteosarcoma.<sup>41</sup> 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 treatments.<sup>34</sup> 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.<sup>34</sup> Sclerostin protects against excessive bone formation.

Studies with monoclonal antisclerostin 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.<sup>34</sup> Additionally, these antibodies stimulated 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.<sup>34</sup>

Subcutaneous injections of the antisclerostin antibody *romosozumab* have been studied in phase I and II trials.<sup>42 43</sup> 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 teriparatide. 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 injections of the antisclerostin antibody *blosozumab* have been

studied in phase I and II trials.<sup>44–45</sup> 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 drugs 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.<sup>46–50</sup> 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.<sup>46–50</sup> None of the studies were powered to study an effect on fracture risk.<sup>50</sup>

**Sequential therapy** of antiresorptives and osteoanabolic treatment has been documented by its effect on BMD.<sup>49</sup> In patients treated with BPs who still develop fractures or still lose BMD, switching to teriparatide is advocated.<sup>49</sup> However, continuing antiresorptive treatment when starting teriparatide resulted in a better response of BMD in the hip.<sup>51</sup> 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 antisclerostin 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%.<sup>52</sup> 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.<sup>53</sup>

**Competing interests** None declared.

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**Data sharing statement** No additional data are available.

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