Novel therapies in benign and malignant bone diseases

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A B S T R A C T

With an ageing population and improving cancer therapies, the two most common benign and malignant bone diseases, osteoporosis and bone metastases, will continue to affect an increasing number of patients. Our expanding knowledge of the molecular processes underlying these conditions has resulted in novel bone targets that are currently being explored in clinical trials. Clearly, the approval of denosumab, a monoclonal antibody directed against RANKL, has just marked the beginning of a new era for bone therapy with several additional new therapies lining up for clinical approval in the coming years. Potential agents targeting the osteoclast include cathepsin K, currently in phase 3 trials, and src inhibitors. Amongst anabolic agents, inhibitors of the Wnt-inhibitor sclerostin and dickkopf-1 are promising in clinical trials. Here, we will provide a comprehensive overview of the most promising agents currently explored for the treatment of bone diseases.

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1. Introduction

For many years, approved therapies for benign bone disease have consisted of only few compounds, namely bisphosphonates, selective estrogen receptor modulators (SERMs), strontium ranelate (not approved in USA) and parathyroid hormone (PTH) (Sambrook and Cooper, 2006). For malignant bone disease, bisphosphonates were the only established pharmacological agent (Schwetz, 2001). While there is solid data to support anti-fracture efficacy and reduction of skeletal related events (SREs) for bisphosphonates, there are a number of conditions, like an impaired renal function, that may limit their use in certain patient subgroups that are at urgent need for bone-protective therapy. An increasing knowledge of the molecular and cellular mechanisms that regulate bone homeostasis and their contribution to bone pathology has led to the identification of promising therapeutic targets (Rachner et al., 2011). Some of these agents are targeting pathways that have been specifically found to be relevant for the development of bone metastases, e.g. Wnt and endothelin signaling by influencing osteoclastic or, in some cases, osteoblastic activity. Others are primarily tested for the treatment of osteoporosis, with a strong focus on concepts to increase osteoblastic bone formation such as sclerostin inhibition. Apart from classic primary and secondary osteoporosis and malignant bone disease, a third group with special requirements regarding their bone

Abbreviations: CaSR, calcium sensing receptor; MBD, myeloma bone disease; RANKL, receptor activator of NF-κB ligand; SREs, skeletal related events; ZOL, zoledronic acid.

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health is now emerging. Improvements in the early diagnosis and adjuvant treatment of breast and prostate cancer have considerably improved the survival of affected patients. However, many of these patients are treated with hormone- ablative therapies that are associated with a substantial decline in bone health (Saad et al., 2008). Cancer treatment induced bone loss (CTIBL) combines classic features of osteoporosis with those of metastatic bone disease with regard to treatment regimes and long-term prognosis.

With the successful approval of denosumab for the treatment of osteoporosis, CTIBL and malignant bone disease in 2010 and 2011, respectively, bone therapy has been provided with its first and widely applicable antibody-based agent (Tsourdi et al., 2011). When looking at the portfolio of available substances for the treatment of bone disease, most current therapies, including denosumab can be considered as classic anti-resorptive agents. These substances prevent bone loss by inhibiting osteoclastic bone resorption and are in most cases effective to prevent further bone loss and fractures. Substances that rebuild bone are referred to as bone anabolic. This effect is generally achieved by activating osteoblastic bone formation at various molecular and cellular levels. Currently, approved bone anabolic agents are limited to the full-length parathyroid hormone (PTH 1–84) or its fragment, teriparatide (PTH 1–34).

This article will present some of the most promising bone protective agents currently explored. We will summarize their molecular mechanisms, pharmacology and highlight key results from clinical trials.

2. Targeting receptor activator of NF-κB ligand

Physiologic bone turnover is tightly controlled by the amount of osteoclastic bone resorption on one side and osteoblastic bone formation on the other side. In a healthy grown-up individual these processes are balanced to secure the constant rate of bone renewal that is needed to preserve bone mass and quality while maintaining its integrity. This process continuously adapts to respond to changing environmental requirements. In this concert of osteoclast–osteoblast–osteocyte interaction, the receptor activator of NF-κB ligand (RANKL) is the major factor defining the level of osteoclast activity. For many years, osteoblasts have been thought to be the main source of RANKL in the bone microenvironment. However, recent results from two independent studies provide evidence that osteocytes are the major contributor for RANKL within bone (Nakashima et al., 2011; Xiong et al., 2011). Upon binding to its receptor RANK, RANKL activates the differentiation, proliferation and activity of osteoclasts, thus determining the level of osteoclastic bone resorption (Hofbauer & Schoppet, 2004). This potent signaling pathway is regulated by the presence of the dimeric glycoprotein osteoprotegerin (OPG). OPG, which is primarily secreted by osteoblasts, can bind and neutralise RANKL and thus act as its decoy receptor (Simonet et al., 1997). The ratio of RANKL to OPG is therefore the essential determinant at the level of bone turnover. In diseases characterized by excessive osteoclastic activity such as osteoporosis and osteolytic bone metastases, bone loss is generally associated with an enhanced RANKL to OPG ratio (Hofbauer & Schoppet, 2004).

The physiological relevance of the RANKL/RANK and OPG system has been documented by the phenotype of OPG-deficient mice, which developed osteoporosis and multiple low-trauma fractures (Bucay et al., 1998). By contrast, over-expression of OPG in transgenic mice results in an increased bone mass and density (Simonet et al., 1997). The role of RANKL and OPG as essential mediators of bone disease has since been established in most forms of primary and secondary osteoporosis (Hofbauer & Schoppet, 2004). In general, RANKL is up-regulated and OPG is suppressed in the presence of substances that are bone catabolic. Vice versa, bone protective substances such as estrogens are known to suppress RANKL and enhance OPG (Eghbali-Fatourechi et al., 2002). Additionally, an over-expression of RANKL has been noted in a range of osteolytic malignancies like myeloma, breast and prostate cancer (Giuliani et al., 2001). Furthermore, RANKL appears to act as a direct chemoattractant for cancer cells, promoting their migration to bone (Jones et al., 2006; Armstrong et al., 2008). More recently, RANKL has been attributed a role in progenit driven carcinogenesis (Schramek et al., 2010).

Initially, the concept of pharmaceutically regulating osteoclast activity by modifying RANKL signaling via treatment with forms of recombinant OPG was pursued. Landmark animal studies suggested that inhibition of RANKL using an OPG-Fc fusion protein is capable of preventing the formation of bone metastases (Capparelli et al., 2000). However, the relatively short half-life of OPG-Fc, concerns regarding auto-antibody formation, and the potential of OPG to bind and block TNF-related apoptosis-inducing ligand (TRAIL) (Emery et al., 1998), a member of the TNF superfamily that selectively induced apoptosis in malignant cells, led to the development of denosumab, a fully human monoclonal antibody directed against RANKL.

2.1. Development of denosumab

Denosumab was initially tested in a single dose placebo controlled phase 1 trial in postmenopausal women (Bekker et al., 2004). Injection of denosumab led to a dose–dependent, rapid and sustained suppression of uNTX (urinary N-telopeptide of type I collagen), a marker of bone resorption. At the highest applied dose of 3 mg/kg there was a mean uNTX decrease of 81% at 6 months. No related serious adverse events were reported in this trial. Denosumab has been found to have a bioavailability of approximately 60% after subcutaneous injection (Sutjandra et al., 2011), a half life of 32 days (Bekker et al., 2004), and serum plasma concentrations of denosumab peak as early as 1 h after injection (Body et al., 2006). Furthermore, denosumab is not degraded via the kidney. Hence, renal impairment does not affect its pharmacokinetics as demonstrated in a retrospective stratification of the FREEDOM trial cohort according to kidney function (except stage 5 CKD, which none of the patients had), where denosumab reduced the fracture risk and was not associated with increased levels of adverse events across all assessed levels of renal impairment (Jamal et al., 2011b). In a phase 2 dose finding trial, denosumab was injected in postmenopausal women with low bone mass every three months at doses of 6 to 30 mg or biannually at doses of 14 to 210 mg and compared to weekly doses of 70 mg alendronate or placebo. Following 12 months of treatment, BMD had increased in the denosumab groups at all measured sites (lumbar spine, total hip and distal third of the radius) compared to losses in the placebo group. The most potent effects were seen at the lumbar spine, where treatment with denosumab resulted in BMD increases of 3.0 to 6.7%, compared to a 4.6% gain with alendronate and a loss of 0.8% in the placebo group (McClung et al., 2006). In a study extension for another 12 months, denosumab continued to improve BMD (4.1% to 8.9% at lumbar spine) (Lewiecki et al., 2007). The pharmacokinetic properties of denosumab were further explored in an additional 24 months extension using different treatment regimes. While continuous long term treatment with denosumab further improved BMD, treatment discontinuation of denosumab resulted in rapid increases of bone resorption markers and a BMD decline of 6.6% at the lumbar spine within a year. There was no increased fracture risk in patients who had discontinued denosumab in the year off treatment. However, patients remained susceptible to denosumab when treatment was restarted (Miller et al., 2008). Some of these patients (n=80) have now been receiving denosumab for 8 years. Over this period, BMD increased by 16.8% at the lumbar spine and by 6.9% at the total hip (McClung et al., 2011). The reversibility of denosumab mediated effects was further confirmed by an off-treatment biopsy study in postmenopausal osteoporosis. After a mean treatment cessation of 21.5 months, all biopsy specimens showed tetracycline labelling, compared to two thirds of subjects under denosumab treatment (Brown et al., 2011).
2.2. Denosumab in osteoporosis

The anti-fracture efficacy of denosumab was evaluated in a pivotal phase 3 (FREEDOM) trial in 7868 women with postmenopausal osteoporosis (Cummings et al., 2009). Subjects were grouped to receive either biannual injections of 60 mg of denosumab or placebo for 3 years. Compared to placebo, treatment with denosumab significantly reduced the fracture incidence of radiographically detectable vertebral (−68%), hip (−40%) and non-vertebral (−20%) fractures (Cummings et al., 2009). In a head-to-head comparison with open-label alendronate (DECIDE trial), denosumab treatment resulted in a BMD increase of 3.5% at the total hip, compared to a 2.6% gain in the alendronate group (p=0.0001). Significantly larger gains were also noted at the femoral neck (+6.6%), trochanter (+1.0%), lumbar spine (+1.1%), and distal radius (+0.6%) (Brown et al., 2009). In addition to its use in postmenopausal osteoporosis, denosumab has been evaluated in patients with treatment induced bone loss secondary to hormone ablation therapies for breast (Ellis et al., 2008) and prostate cancer (Smith et al., 2009). In 252 women with breast cancer receiving aromatase inhibitor treatment, the administration of denosumab resulted in a BMD increase of 5.5% at the lumbar spine (Ellis et al., 2008). In a larger trial in men with non-metastatic prostate cancer (HALT trial), 1468 men were randomised to receive denosumab or placebo for 24 months. Here, denosumab proved to be effective in increasing BMD at the lumbar spine after 24 months (primary endpoint) by 5.6%, compared to a loss of 1% in the placebo group (Smith et al., 2009). Furthermore, this trial was the first to demonstrate a significant reduction in new vertebral fractures for denosumab in patients undergoing hormone ablation therapy; 1.5% compared to 3.9% with placebo after 36 months (p=0.006).

2.3. Denosumab in malignant bone disease

Three large head-to-head trials compared denosumab to zoledronic acid, in most countries the current treatment standard in metastatic bone disease. In analogy to zoledronic acid (4 mg every 4 weeks), the dosing interval of denosumab is shorter in bone metastases and a monthly dose of 120 mg is used. In patients suffering from bone lesions secondary to breast cancer, denosumab proved to be non-inferior (primary endpoint) and superior (secondary endpoint) to zoledronic acid in delaying the time-to-first and time-to-first-and-subsequent SRE by 18% and 23%, respectively (Stopeck et al., 2010). Suppression of bone metastases secondary to breast cancer, denosumab proved to be effective in increasing BMD at the lumbar spine after 24 months (primary endpoint) by 5.6%, compared to a loss of 1% in the placebo group (Smith et al., 2009). Furthermore, this trial was the first to demonstrate a significant reduction in new vertebral fractures for denosumab in patients undergoing hormone ablation therapy; 1.5% compared to 3.9% with placebo after 36 months (p=0.006).

2.4. Safety and tolerability of denosumab

Overall, denosumab has been proven to be well tolerated in the osteoporosis setting (60 mg every 6 months) as well as for the treatment of bone metastases (120 mg every month). However, a number of adverse events were significantly increased in some of the above mentioned trials. In the FREEDOM trial, patients receiving denosumab had increased rates of dermal events (eczema and cellulitis) (Cummings et al., 2009). Men receiving denosumab in the HALT trial, had increased rates of cataracts compared to those receiving placebo (4.7% vs. 1.2%). While close monitoring for these reactions in the relevant groups appears reasonable, it should be noted, that these adverse events were not observed in other trials and a causal link to denosumab has not been established. Furthermore, immunological testing of patients receiving denosumab for osteoporosis could not detect any abnormalities with respect to haematopoietic or immune function and infectious defence (Stolina et al., 2007). In patients receiving denosumab for the treatment of bone metastasis secondary to breast or prostate cancer, hypocalcemia appeared with an incidence of 9.6% (Hadji, 2011). While these episodes were generally transient, regular monitoring of serum calcium levels should be conducted in those patient groups and if needed adequate supplementation be supplied. With an incidence of 0.1% (HALT trial) or less, hypocalcemia does not appear to be a relevant problem when given for the treatment of osteoporosis, if calcium levels are normal prior to denosumab and vitamin D supplementation is adequate. In the past, the association of osteonecrosis of the jaw (ONJ) with the administration of bisphosphonates has received considerable public and scientific attention. Results may have limited the value of this study. Other reasons for these results, such as the potential overproportion of RAS mutations in myeloma patients, which may be more effectively targeted by zoledronic acid (via inhibition of the mevalonate pathway), have also been proposed (Sorscher & Lockhart, 2011). These unclear results have led to denosumab not receiving an FDA approval for the treatment of myeloma disease (Table 1). To resolve the current uncertainties, a large trial is currently recruiting myeloma patients to reassess the potential of denosumab in this entity (NCT01345019). While the above trials have established denosumab for the treatment of bone metastases, emerging results from basic and translational research are proposing an important contribution of RANKL to the metastatic process of breast and prostate cancer cells. This notion is supported by recent results from a phase 3 trial in men with non-metastatic castration-resistant prostate cancer with a high risk of developing bone metastasis. (NCT00286091). Denosumab significantly prolonged bone-metastasis-free survival by a median of 4 months compared to placebo (29 vs. 25 months; 95% CI 0.73–0.98, p=0.028). Overall survival did not differ between groups and as many of 5% of patients receiving denosumab developed ONJ compared to none in the placebo group (Smith et al., 2012). Denosumab, for the prevention or delay of bone metastases in women with high-risk breast cancer is currently evaluated in another phase 3 trial (NCT01077154).

Table 1
Pharmacological characteristics of denosumab.

<table>
<thead>
<tr>
<th>Approved for</th>
<th>PMO</th>
<th>CTIBL</th>
<th>Bone metastases due to solid tumors (not for multiple myeloma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Prolia</td>
<td>Xgeva</td>
<td>Xgeva</td>
</tr>
<tr>
<td>Dosing regime</td>
<td>60 mg q 6 months</td>
<td>120 mg q 4 weeks</td>
<td>Xgeva</td>
</tr>
<tr>
<td>Fx/SRE reduction vs. zoledronic acid</td>
<td>Yes</td>
<td>Yes</td>
<td>Superior in breast and prostate cancer Not superior in MM</td>
</tr>
</tbody>
</table>

Type of agent: fully human monoclonal antibody

Route of administration: subcutaneous injection
from the large head-to-head trials for malignant bone disease suggest that ONJ occurs with a comparable frequency in patients receiving zoledronic acid (1.4%) and denosumab (2.0%) (Hadji, 2011). While the exact underlying mechanisms of ONJ are still unknown, a number of simple measures have been proposed to minimize the risk of ONJ (Khan et al., 2008). Furthermore, results from the above studies underline the idea that ONJ may not be an agent specific effect, but may rather be a potentially inevitable mechanistic effect closely associated with potent suppression of bone turnover. It is now generally accepted that the risk of ONJ as a result of bisphosphonate treatment in the osteoporosis setting is relatively low. In accordance, no cases of ONJ were observed in the initial evaluation of the FREEDOM and HALT trials, but two cases of ONJ have been reported in an open label extension of the FREEDOM trial. Considering the large number of patients receiving denosumab in these trials, ONJ can still be considered a very rare event in the osteoporosis setting.

2.5. Emerging strategies

In addition to denosumab, a number of other promising bone targets are currently evaluated at different stages in clinical trials. These agents present a heterogeneous group with different cellular targets and distinct pharmacological properties (summarized in Table 2 and Fig. 1). Cathepsin K and src kinase are two osteoclastic targets, with encouraging in vitro and in vivo data. Recent data indicates that nitroglycerin, a well established drug for symptomatic treatment of coronary artery disease, may also have profound anti-resorptive effects. All three agents have in common that they may have uncoupling effects (Rachner et al., 2011; Rejnmark & Mosekilde, 2011). Physiologically, osteoclastic bone resorption is coupled with osteoblastic bone formation. Established anti-resorptive substances commonly affect osteoclast vitality, preventing paracrine osteoclast-osteoblast signaling. As a consequence, the anti-resorptive activity of classic anti-resorptives is associated with a decreased bone formation based on the decline of biochemical markers of bone formation. Current biomarker-based data indicates that some of these novel agents lack suppressive effects on bone formation markers, and, thus may confer an uncoupling potential. However, the clinical consequence of these findings still requires validation, in particular whether these effects translate into meaningful clinical benefits, e.g. a lower risk of ONJ with sustained anti-fracture or anti-SRE efficacy.

3. Targeting cathepsin K

The process of osteoclastic bone resorption is largely mediated by cathepsin K, a lysosomal proteinase that is expressed and secreted by mature osteoclasts. In the resorption lacunae below the osteoclast, cathepsin K is activated by the acidic milieu to degrade components of the bone matrix, in particular type I collagen. The physiological relevance of cathepsin K is emphasized by the finding that cathepsin K-deficient mice develop osteopetrosis (Saftig et al., 1998). In humans, a genetic mutation of cathepsin K causes pycnodysostosis, an infrequent medical condition, characterized by short stature, short distal phalanges, prominent head and nose, a small jaw and osteosclerosis, predisposing to recurrent fractures (Gelb et al., 1996). It is thought that the French painter Henri de Toulouse-Lautrec suffered from pycnodysostosis; hence this condition is sometimes referred to as the Toulouse–Lautrec syndrome.

3.1. Odanacatib

Odanacatib is an orally delivered, highly selective, cathepsin K inhibitor that was initially evaluated in two phase 1 studies in postmenopausal women (Stoch et al., 2009). Applied at weekly or daily doses for three weeks, the pharmacokinetic analyses revealed a half life of 66–93 h, compatible with a once weekly administration. Both weekly and daily doses substantially reduced serum CTX by 62% and 82%, respectively. Odanacatib was generally well tolerated. Importantly, no scleroderma-like lesions were seen. This off-target effect had previously led to the discontinuation of other less specific cathepsin inhibitor programs that showed a certain affinity for other cathepsins like B, L and S (Peroni et al., 2008). A phase 2 dose-finding trial assessed odanacatib in 399 women with postmenopausal osteoporosis (Bone et al., 2010). After two years, dose dependent gains in BMD were observed, with weekly doses of 50 mg odanacatib resulting in BMD increases of 5.5% and 3.2% at the lumbar spine and total hip compared to losses of 0.2% and 0.9% in the placebo group (Bone et al., 2010). In a one-year extension trial, 189 women of the initial trial were re-randomized to receive weekly doses of odanacatib (50 mg) or placebo (Eisman et al., 2011). Patients who had received 50 mg doses of odanacatib for the whole 3 years showed significant BMD increases at the spine and total hip compared to baseline (+7.9% and +5.8%, respectively) and increases of 2.3% and 2.4% compared to year two. Cessation of treatment after 2 years and administration of placebo in the third year resulted in a strong bone loss at all sites and a massive, although transient, increase of bone resorption markers above baseline (serum N-telopeptide of type I collagen increase by 230%).

The expression of cathepsin K in prostate and breast cancer (Littlewood-Evans et al., 1997; Brubaker et al., 2003) suggests an involvement in the development of bone metastases. Inhibition of cathepsin K successfully reduced the tumor burden in a murine breast cancer model (Le Gall et al., 2007). While results from a head-to-head trial with zoledronic acid in women with bone metastases were encouraging, with a comparable reduction of uNtx after 4 weeks (77% vs. 73%) (Jensen et al., 2010), the study program for the use of odanacatib for malignant bone diseases is currently no longer active. Results from a pivotal phase 3 trial (NCT 00529373) to test odanacatib in women with postmenopausal women are expected later this year.

4. Nitroglycerin

A number of preclinical in vitro and in vivo studies have proposed that nitric oxide inhibits osteoclast activity and affects osteoblast and osteocyte signaling. Nitric oxide, as found in nitroglycerin, is a well established, inexpensive and widely available drug. Thus, its potential use for the treatment of osteoporosis poses an intriguing idea. Early clinical data from observational studies, suggests that nitrates reduce the fracture rate in women (Rejnmark et al., 2006) and that women with intermittent nitrate exposure have a higher bone mineral density compared to nonusers and those using nitrates continuously (Jamal et al., 1998). Results from two randomized controlled trials yielded different results. While one reported of decreased bone resorption and increased formation markers after once daily application of isosorbide nitrate (Jamal et al., 2004), another study failed to find increases in BMD following 36 months of nitroglycerin use (Wimalawansa et al., ...
Sclerostin antibodies (AMG 785) were successfully tested in a rodent bone mass. Neutralizing monoclonal antibodies directed against the gene, which encodes for sclerostin, result in progressive pathological bone thickening and clinical conditions named sclerosteosis and van Buchem’s disease (Balemans et al., 2001; Loots et al., 2005). Further- more, SOST−/− mice have an increased bone formation and high bone mass. Thus, neutralizing monoclonal antibodies directed against sclerostin were generated. These were successfully tested in a rodent model of postmenopausal osteoporosis, where the application of the sclerostin antibody for a period of 5 weeks resulted in pronounced bone anabolic effects (Li et al., 2009). Similar positive effects were reported in a study with cynomolgus monkeys (Ominsky et al., 2010). Sclerostin antibodies (AMG 785) were first tested in 72 healthy adults in a single-dose phase 1 study (Padhi et al., 2011). AMG 785 was applied either via subcutaneous or intravenous injections in ascending doses. After 85 days a subcutaneous dose of 10 mg/kg had increased the BMD at the lumbar spine (5.3%) and total hip (2.8%). An intravenous dose of 5 mg/kg increased the lumbar spine BMD by 5.2% and BMD at the total hip by 1.1%. In both treatment groups, AMG 785 dose-dependently increased the bone formation markers P1NP, BAP and osteocalcin. AMG 785 was generally well tolerated. One patient who received the highest subcutaneous dosing (10 mg/kg) reported a severe hepatitis one day after injection. Of note, six of the 54 patients receiving AMG 785 developed antibodies, two of which were neutralizing. Scleros- tin antibodies are currently compared to open label alendronate and teriparatide in an ongoing multi-dose phase 2 trial in women with post-menopausal osteoporosis (NCT00896532).

5.2. Dickkopf-1 antibody (BHQ 880)

Elevated DKK-1 serum levels have been associated with the presence of bone lesions in patients with multiple myeloma, lung and breast cancer and DKK-1 inhibition has been shown to successfully prevent the formation of bone lesions in preclinical models of metastases (Fulciniti et al., 2009). DKK-1 antibodies are under evaluation in phase I and II trials for patients with multiple myeloma (NCT00741377, NCT01302886 and NCT01337752).

6. Targeting calcium sensing receptor (Calcilytics)

Physiologically the release of PTH is strongly regulated as a response to activation via the calcium sensing receptor (CaSR) to maintain calcium homeostasis. Activators of the CaSR, named calcimimetics have been successfully developed to mimic hypocalcaemia and consequently down-regulate PTH secretion in primary and secondary hyperthyroidism. A bone anabolic approach is to antagonize the CaSR using calcilytic drugs, mimicking hypocalcemia and thus causing a transient increase of PTH. A phase I and II trial for patients with multiple myeloma (NCT00741377, NCT01302886 and NCT01337752).

Fig. 1. Novel bone agents.
6.1. MK-5442

At present, several calcitriols with more favourable pharmacologic properties are assessed in clinical trials (Balan et al., 2009; Kumar et al., 2010). The most advanced, MK-5442 is an oral calcitriol which has been evaluated in two phase 2 trials in (NCT00996801 and NCT00960934) approximately 900 postmenopausal women. These trials have been completed and results have not yet been published. However, because of continuous hyperparathyroidism-like condition, this agent will no longer be pursed in future trials.

7. Targeting endothelin

Endothelin (ET) signaling is a proposed target in osteoblastic bone metastases, as commonly seen in patients with advanced prostate cancer. ET-1 is overexpressed in many malignancies and ET-1 activates osteoblasts directly and indirectly by inhibiting Dkk1 (Clines et al., 2007). While preclinical testing of ET-A receptor inhibition using atra-sentan appeared promising in reducing the tumor-induced osteoblast response in mice inoculated with ZR-75-1 cells (Yin et al., 2003), results from phase 2 and 3 trials have yielded inconsistent results (Carducci et al., 2003; Nelson et al., 2008). In another phase 2 study, co-treatment of atrasentan and zolendronic acid in men with bone metastases secondary to prostate cancer did not have synergistic effects on markers of bone metabolism (Michaelson et al., 2006). Other combination trials (atra-sentan and docetaxel) are ongoing (NCT00134056) to clarify potential of endothelin inhibiting strategies in MBD.

8. Targeting activin A (ACE 011)

Activin A, best known for its role in regulating FSH release from the pituitary, also promotes osteoclasts and inhibits osteoblasts. Furthermore, activin A appears elevated in patients with osteolytic bone disease (breast, prostate and myeloma) (Leto et al., 2006; Vallet et al., 2010).

In a preclinical murine model of human breast cancer and multiple myeloma, inhibition of activin A prevented cancer induced bone destruction (Chantry et al., 2010; Vallet et al., 2010). The efficacy of ACE-011, an activin A inhibitor, to rapidly and sustainably increase bone-specific alkaline phosphatase by up to 36% (p<0.01) has been documented in a phase 1 trial in postmenopausal women (Ruckle et al., 2009). ACE-011 is currently evaluated in a phase 2 trial in patients with multiple myeloma bone disease (NCT00747123).

9. Discussion

Considerable progress has been made in understanding the multi-ple molecular pathways that define bone metabolism by regulating osteoclasts, osteoblasts and osteocytes. With the approval of denosumab, a novel and effective anti-resorptive agent has evolved as a valid alternative to established therapies for both malignant and benign bone disease. In light of the diversity of substances currently under evaluation for benign (odanacatib, AMG-785 and MK-5442) and malignant (BHQ-880, atrasentan and ACE-011) bone conditions, our repertoire will further expand. Novel therapeutic approaches are aimed to be highly specific and associated with a higher level of patient comfort compared to currently employed treatment modalities. In this context, two classes of drugs will be especially attractive for the osteoporosis setting: osteoblast targeting anabolic agents and “osteoblast-friendly” uncoupling anti-resorptives.

Will the bone specialist be spoilt for choice? Clearly, the differential benefits of these substances require clinical validation and integration into the long-term and sequential treatment concept of osteoporosis and bone metastases, in order to achieve improved patients care. While the idea of having a wide spectrum of novel bone modulating agents available is tempting, their appropriate use will concurrently require a much greater knowledge and application of bone biology.

Conflict of interest

LCH has received honoraria from Amgen, Merck, Novartis, and Nycomed. PH has received honoraria from Amgen, Astra Zeneca, Daichii Snakyo, Eli Lilly, Novartis, Nycomed, Pfizer and Roche. TDR has no conflict of interest.

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