Osteoporosis in thalassaemia

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Abstract

Osteoporosis is a prominent cause of morbidity in patients with thalassaemia major (TM) with a complex pathophysiology. Patients with TM and osteoporosis have elevated markers of bone resorption. This increased osteoclast activity seems to be at least partially due to an imbalance in the receptor–activator of nuclear factor-kappa B ligand (RANKL)/osteoprotegerin (OPG) system, which is of great importance for the regulation of osteoclast differentiation and function. Denosumab is a fully human monoclonal antibody that binds to RANKL and thereby inhibits the activation of osteoclasts by RANKL. By blocking RANKL, denosumab inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass in postmenopausal women and patients with thalassaemia-induced osteoporosis.

Introduction

Osteoporosis is a prominent cause of morbidity in patients with thalassaemia major (TM) and has complex pathophysiology (1). Therefore, the necessity of understanding the underlying mechanisms for bone destruction in these patients seems to be compulsory.

Recent identification of novel markers of bone remodeling and osteoclast function has significantly contributed in understanding the pathophysiology of the disease.

Although osteoblast dysfunction is thought to-date to be the major pathogenetic mechanism for osteoporosis in TM, there is also evidence of increased osteoclast activation in these patients. Both Dresser Pollack et al (2000) (2) and our group have shown that patients with TM and osteoporosis have elevated markers of bone resorption, such as urinary levels of N-terminal crosslinking telopeptide of collagen type I (NTX), which is a specific marker of bone resorption, and increased serum levels of tartrate resistant acid phosphatase isoform 5b (TRACP-5b), an enzyme that is produced only by activated ostoclasts (3). The RANK/RANKL/OPG system seems to be of great importance for the activation and proliferation of osteoclast precursors. We and others have previously shown that RANKL, the most potent osteoclast activator, is elevated in the serum of TM patients and correlates with reduced bone mineral density (BMD) (3, 4). The increase of RANKL, followed by unmodified OPG levels, with the consequent increase of RANKL/OPG ratio may represent a major cause of uncoupling bone turnover observed in thalassaemia patients.

The increased bone resorption observed in TM patients with osteoporosis has led to the use of bisphosphonates (inhibitors of osteoclast function) in the management of osteoporosis in this cohort of patients (3, 5, 6). Both oral (alendronate) and intravenous (pamidronate, zoledronic acid) bisphosphonates have been used in TM patients with the intravenous ones to show the highest efficacy (1). However, a novel monoclonal antibody (denosumab) which targets RANKLis now available for osteoporosis patients and thus it is of great importance to know its efficacy in thalassaemia patients with osteoporosis.

Mechanism of action of denosumab

Osteocyte is the key cell for starting bone remodeling. In cases of microcracks they release RANKL, which binds to RANK on osteoclasts and osteoclast precursors, activating osteoclasts that resorb the destroyed bone.

Denosumab is a fully human monoclonal antibody that binds to RANKL and thereby inhibits the activation of mature osteoclasts by RANKL and prevents the maturation of osteoclast precursors and multinucleated osteoclasts (7).

It has a circulatory half-life of approximately 26 days, and like other monoclonal antibodies, the clearance of denosumab is through the reticuloendothelial system and does not depend on renal clearance. By blocking RANKL, denosumab inhibits osteoclast formation, function and survival, and thus it decreases bone resorption and increases bone mass and bone strength in both cortical and trabecular bone.

On the contrary, bisphosphonates do not inhibit osteoclast formation but they lead to their apoptosis through their binding into hydroxyapatite and their internalization by osteoclasts during the resorption process.

In addition, other biological inhibitors of the RANK/RANKL pathway, such as OPG linked to an immunoglobulin crystallizable fragment (OPG-Fc) and RANK linked to an immunoglobulin crystallizable fragment (Fc), were used to evaluate the pharmacodynamic properties of denosumab in rodent models. These studies show that denosumab is a potent inhibitor of bone resorption via inhibition of RANKL.

Clinical experience

Denosumab 60 mg every 6 months has been generally well tolerated in clinical studies. In FREEDOM study, there were no significant differences between subjects who received denosumab and those who received placebo over 36 months, in the total incidence of adverse events, serious adverse events, or discontinuation

of study treatment because of adverse events (8). Long term treatment, for up to 7 years, remained well tolerated and was associated with maintaining low incidence of clinical fractures. Denosumab has been licensed for the treatment of postmenopausal osteoporosis, as clinical data confirm that it leads to significant increases in BMD, with decreased risk of vertebral, hip and non-vertebral fractures. It has a very good renal safety profile in contrast to 3rd generation BPs (*i.e.* zoledronic acid), which need dose modifications according to CrCl.

The effects of denosumab on TM- induced osteoporosis

However, there are no prospective data for the effects of denosumab on TM- induced osteoporosis. Our center, evaluated the efficacy of denosumab in patients with thalassemia and osteoporosis in a randomized, placebo-controlled, double blind, single-site, phase 2b clinical trial.

The primary objective of this study was to evaluate the results of denosumab on lumbar spine (L1-L4) BMD in patients with TM and osteoporosis as compared to placebo at 12 months, while secondary endpoints included the evaluation of the effects of denosumab on femoral neck (FN) and wrist (WR) bone mineral density (BMD) at 12 months, the evaluation of the safety profile of denosumab as well as its effects on bone turnover markers. The main inclusion criteria included: adult patients (>30 years of age) with TM and BMD T-score between -2.5 and -4.0 in at least one of the examined sites (L1- L4, FN, WR). The main exclusion criteria included: impaired renal function (eGFR of ≤30 mL/min), elevated ALT and/or AST >2 fold the upper limit of normal (UNL), heart failure (NYHA above 2), administration of bisphosphonates within one year of study enrolment and the presence of any other disorder that affects bone metabolism. Patients were assigned into two treatment groups: in group A, 60 mg Denosumab was administered sc, every 6 months for 12 months for a total of 2 doses (day 0 and day 180); in group B, placebo was administered sc, at the same time. All patients received calcium and vitamin D supplementation. Measurement of BMD with dual energy X-ray absorptiometry at three body sites (L1-L4, FN, WR) was performed during the screening period and at the end of the study. The following biochemical markers were evaluated on the day 0 and then every 3 months up to 12 months (every patient had 5 measurements): i) osteoclast regulators: sRANKL and osteoprotegerin (OPG); ii) osteoblast inhibitors dickkopf-1 (Dkk-1) and sclerostin (SOST); iii) bone resorption markers: C-telopeptide of collagen type-I (CTX) and TRACP-5b; and iv) bone formation markers: bone-specific alkaline phosphatase (bALP) and osteocalcin.

Patients of group A (denosumab arm) achieved an increase in both L1-L4 BMD (p<0.001) and FN BMD (p=0.022), while there were no changes in WR BMD. Patients of group B (placebo arm) achieved a slight increase in their L1-L4 BMD and a significant decrease in their WR BMD (p=0.008). The percentage increase of L1-L4 BMD was higher in denosumab arm than in placebo arm (6.02±5.30% *vs* 3.11±5.46%, respectively; p=0.03), while the advantage of denosumab regarding WR BMD was much higher compared to placebo (-0.22±5.40% *vs* -4.15±8.58%, respectively; p=0.02). No grade 3 or 4 toxicity was observed in this study. Patients who received denosumab showed a dramatic reduction of

sRANKL, sRANKL/OPG ratio, CTX, TRACP-5b, bALP between baseline and 12th month (p<0.01 for all comparisons) without changes in Dkk-1, SOST and OC. On the contrary, placebo patients showed an increase in sRANKL, OPG, Dkk-1, CTX, TRACP-5b, bALP during the study period (p<0.01 for all comparisons) along with a slight increase of SOST and OC (p=NS).

In conclusion, denosumab, given twice per year in TM patients with osteoporosis, increases the BMD of the L1-L4 more efficiently than placebo after 12 months, with excellent safety profile. Denosumab also reduced markers of bone resorption and osteoclast activation without affecting Dkk-1, which was increased in placebo arm patients in whom there was a significant increase in osteoclast activators and both bone resorption markers. These data support the use of denosumab for the management of TM-induced osteoporosis. However, studies with larger number of patient with thalassaemia induced osteoporosis are needed for evaluating the efficacy and long-term safety in these patients.

References

1. Voskaridou E, Terpos E. New insights into the pathophysiology and management of osteoporosis in patients with beta thalassaemia. Br J Haematol. 2004;127:127-39.
2. Dresner Pollack R, Rachmilewitz E, Blumenfeld A, Idelson M, Goldfarb AW. Bone mineral metabolism in adults with beta-thalassaemia major and intermedia. Br J Haematol. 2000 Dec;111(3):902-7.
3. Voskaridou E, Terpos E, Spina G, Palermos J, Rahemtulla A, Loutradi A, Loukopoulos D. Pamidronate is an effective treatment for osteoporosis in patients with beta-thalassaemia. Br J Haematol. 2003;123:730-7.
4. Morabito N, Gaudio A, Lasco A, Atteritano M, Pizzoleo MA, Cincotta M, La Rosa M, Guarino R, Meo A, Frisina N. Osteoprotegerin and RANKL in the pathogenesis of thalassemia-induced osteoporosis: new pieces of the puzzle. J Bone Miner Res. 2004;19:722-7.
5. Morabito N, Lasco A, Gaudio A, Crisafulli A, Di Pietro C,Meo A, *et al.* Bisphosphonates in the treatment of thalassemia-induced osteoporosis. Osteoporos Int 2002;13:644-9.
6. Pennisi P, Pizzarelli G, Spina M, Riccobene S, Fiore CE. Quantitative ultrasound of bone and clodronate effects in thalassemia-induced osteoporosis. J Bone Miner Metab 2003; 21:402-40
7. Elliot R, Kostenuik P, Chen C, *et al.* Denosumab is a selective inhibitor of human receptor activator of NF-κβ ligand that blocks osteoclast formation *in vitro* and *in vivo*. Eur J Ca Suuppl. 2006;4:62.
8. Cummings SR, San Martin J, McClung MR, et al; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009 Aug 20;361(8):756-65.
9. Voskaridou E, Papaefstathiou A, Christoulas D, Dimopoulou M, Repa K, Papatheodorou A, Peppa M & Terpos E. Denosumab Increases Bone Mineral Density In Patients With Thalassemia Major And Osteoporosis: Results Of A Randomized, Placebo-controlled, Double Blind, Phase 2b Clinical Trial. Haematologica 2017, Vol. 102, p. 16. [abstract; 22nd Congress of the European Hematology Association, Madrid, Spain, 22-25 June 2017].