Maturitas xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Mini Review

Anti-sclerostin antibodies: Utility in treatment of osteoporosis

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ARTICLE INFO

Article history:
Received 22 April 2014
Accepted 23 April 2014
Available online xxx

Keywords:
Romosozumab
Blosozumab
Sclerostin
Anti-sclerostin antibody
Osteoporosis
Treatment

ABSTRACT

Monoclonal antibodies to molecular targets important for bone formation and bone resorption are being investigated for treatment of postmenopausal osteoporosis. Postmenopausal osteoporosis is characterized by increased bone turnover, with bone resorption typically exceeding bone formation. These pathophysiological changes cause decreased bone mineral density and disruption of bone microarchitecture which lead to low-trauma fractures.

Sclerostin is a glycoprotein inhibitor of osteoblast Wnt signaling produced by osteocytes that has been recognized as a new target for therapeutic intervention in patients with osteoporosis. Sclerostin was first recognized when disorders with inactivating mutations of the sclerostin gene SOST were found to be associated with high bone mass. These observations suggested that inhibitors of sclerostin might be used to increase bone mineral density.

Romosozumab (AMG 785) is the first humanized anti-sclerostin monoclonal antibody that has been demonstrated to increase bone formation. This investigational monoclonal antibody, and blosozumab, another investigational anti-sclerostin antibody, have osteoanabolic properties with the potential to improve clinical outcomes in patients with osteoporosis. Similar to preclinical animal studies with sclerostin antibodies, initial clinical studies have shown that romosozumab increases bone formation and BMD. Further evaluation of the efficacy and safety of this agent in a large phase III controlled study is awaited. Phase I clinical trial data have recently been published with blosozumab. These novel interventions appear to be promising agents for the treatment of osteoporosis.

Contents

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http://dx.doi.org/10.1016/j.maturitas.2014.04.016
0378-5122/

1. Introduction

Postmenopausal osteoporosis is a disorder characterized by high bone turnover, with bone resorption exceeding bone formation, which results in decreased bone mineral density (BMD) and disruption of bone microarchitecture leading to fragility fractures [1,2]. Sclerostin is a glycoprotein inhibitor of osteoblast Wnt signaling produced by osteocytes that has been recognized as a newly identified target for therapeutic intervention in patients with osteoporosis [3]. Sclerostin was first recognized as a molecular target for treatment of osteoporosis when disorders with inactivating mutations of the sclerostin gene SOST were found to be associated with high bone mass [4,5]. These observations suggested that inhibitors of sclerostin might be used to increase BMD.

Romosozumab (AMG 785) is the first humanized anti-sclerostin monoclonal antibody that has been shown to increase bone formation. This investigational monoclonal antibody, and blosozumab, another investigational anti-sclerostin antibody, have osteoanabolic properties with the potential to improve clinical outcomes in patients with osteoporosis. Similar to preclinical animal studies with sclerostin antibodies, initial clinical studies have shown that romosozumab increases bone formation and BMD. Further evaluation of the efficacy and safety of this agent in a large phase III controlled study is awaited. Phase I clinical trial data have recently been published with blosozumab.

This mini-review summarizes the published data on the anti-sclerostin antibodies romosozumab and blosozumab. Most of the studies reviewed focus on romosozumab because this agent is farther along in the development process. These novel interventions appear to be promising agents for the treatment of osteoporosis.

2. Romosozumab

2.1. Phase II study

A phase II, multicenter, international, randomized, placebo-controlled, parallel-group, eight-group study evaluated the efficacy and safety of romosozumab over 12 months in 419 postmenopausal women aged 55–85 years who had low BMD [6]. Low BMD was defined as a T-score of −2.0 or less at the lumbar spine, total hip, or femoral neck, and −3.5 or more at each of the three sites. Participants received monthly doses of 70 mg, 140 mg, or 210 mg of subcutaneous romosozumab, or 3-monthly doses of 140 mg or 210 mg of subcutaneous romosozumab, subcutaneous placebo, the open-label active comparator oral alendronate at 70 mg weekly, or subcutaneous teriparatide at 20 μg each day. The primary end point was the percentage change from baseline in BMD at the lumbar spine at 12 months. Secondary end points included percentage changes in BMD at other sites and in markers of bone turnover. All dose levels of romosozumab were associated with significant increases in BMD at the lumbar spine, including an increase of 11.3% with the 210-mg monthly dose, as compared with a decrease of 0.1% with placebo, and increases of 4.1% with alendronate and 7.1% with teriparatide. Romosozumab was also associated with large increases in BMD at the total hip and femoral neck, as well as transient increases in bone formation markers and sustained decreases in a bone-resorption marker. Adverse events were similar among treatment groups, except for mild injection-site reactions with romosozumab that generally did not recur.

The accompanying commentary to this phase II study by Becker [7] noted that, compared with baseline, BMD was significantly improved for all doses of romosozumab and at all sites except at the distal third of the radius, which remained essentially unchanged. The commentary emphasized that, at the highest monthly dose of romosozumab, increases in BMD at the spine and hip were rapid and robust, surpassing the BMD increase seen with alendronate and teriparatide at 6 months. These increases remained significantly higher than the BMD values with either alendronate or teriparatide by the end of the trial. One of the surprises of the study was that the changes in bone turnover markers were unexpected. Levels of bone-formation markers increased rapidly after the first dose of romosozumab, but then declined, and by month 6, bone-formation markers were nearly back to baseline despite continued treatment. Markers of bone resorption surprisingly declined during the first week and remained suppressed for the duration of the trial. These findings suggested that romosozumab simultaneously transiently stimulated new bone formation and chronically suppressed bone resorption over the 12-month study interval, which is unprecedented among available single-agent therapies for osteoporosis. Combination therapy with teriparatide and potent but intermittently dosed antiresorptive agents such as zoledronic acid [8] or denosumab [9] administered one or two times per year has shown promising similar results.

It is not yet clear that the impressive changes in BMD seen with romosozumab will lead to fracture reduction. Safety of longer-term treatment is also not yet known. Significant stimulation of bone formation over more than one year could potentially cause or worsen skeletal complications such as compression neuropathies or spinal stenosis. The optimal duration of treatment is not yet known. The phase III 3-year clinical trial with romosozumab in postmenopausal osteoporotic women (ClinicalTrials.gov #NCT01631214) will hopefully answer these questions.

2.2. Phase I studies

Padhi et al. [10] performed a double-blind, placebo-controlled, randomized, ascending multiple-dose study with 32 postmenopausal women and 16 healthy men with low BMD over 12 weeks. Women received six doses of 1 or 2 mg/kg once every 2 weeks, or three doses of 2 or 3 mg/kg once every 4 weeks, or placebo, and men received 1 mg/kg once every 2 weeks, or 3 mg/kg once every 4 weeks, or placebo. Mean serum romosozumab exposure increased approximately proportionately to the dose received. Romosozumab increased the bone formation marker serum type 1 aminoterminal propeptide (PINP) by 66–147%, decreased the bone resorption marker serum C-telopeptide (sCTX) by 15–50%, and increased lumbar spine BMD by 4–7%. Two subjects developed neutralizing antibodies without discernable effects on pharmacokinetics, pharmacodynamics, or safety. Adverse event rates were balanced between groups without any significant safety findings.

Padhi et al. [11] performed the first in-human phase I study with romosozumab (AMG 785) in healthy men and postmenopausal women. In this randomized, double-blind, placebo-controlled, ascending, single-dose study, 72 healthy subjects received AMG

Please cite this article in press as: Clarke BL. Anti-sclerostin antibodies: Utility in treatment of osteoporosis. Maturitas (2014), http://dx.doi.org/10.1016/j.maturitas.2014.04.016