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Review Article

Orthopaedics Section

Therapeutic Drug Review on Romosozumab: The First Sclerostin Inhibitor

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ABSTRACT

Osteoporosis is a progressive skeletal disorder which is characterised by low bone mass, normal mineralisation and abnormal bone microarchitecture. This disruption of bone microarchitecture causes subsequent increase in bone fragility and raises risk of fractures. Osteoporosis is a growing public health problem and affects approximately over 200 million people worldwide. In the United Kingdom, it is estimated that around 3 million people have osteoporosis. Since the evolution of drug therapy for osteoporosis in the 1940's with oestrogen therapy several approaches to developing novel therapeutics for osteoporosis in animal studies and clinical observations (e.g., oestrogen, calcitonin, and teriparatide) or opportunistic repurposing of existing compounds (e.g., bisphosphonates) to one driven by advances in fundamental bone biology (e.g., denosumab). The advent of biologic agents has provided a more specific and targeted approach to the treatment of osteoporosis. Sclerostin is a glycoprotein secreted by osteocytes and regulates bone metabolism by inhibiting activation of osteoblast function and bone formation. By inhibiting sclerostin, targeted therapeutic pharmacological agents are being developed to address severe osteoporosis and patients who do not respond well to primary line of medical management of osteoporosis. Romosozumab is humanised as a monoclonal antibody designed to target sclerostin. This review assesses the mechanism and current role of romosozumab in osteoporosis treatment.

Keywords: Antibodies, Bone density, Bone density conservation agents, Monoclonal, Osteocytes, Osteoporosis, Therapy

INTRODUCTION

Osteoporosis is defined as having a Bone Mineral Density (BMD) that is 2.5 standard deviations or more below the average value for young healthy adults (usually referred to as a 'T-score' of -2.5 or lower) [1]. Pharmacological drugs available for the treatment of osteoporosis can be divided into two categories: antiresorptive (or anticatabolic) and anabolic (bone forming) agents. Medical management of osteoporosis usually follows the recommended guidelines [2]. Bone-forming agents are used for shorter durations of treatment, often in patients at extremely high risk of fracture, whereas antiresorptive agents are used as long-term treatments and sometimes after bone-forming agents [3]. Typical medications are initiated depending on intervention thresholds defined using age, T-score and several risk factors.

Clinical prediction tools such as Fracture Risk Assessment Tool (FRAX), osteoporosis self-assessment tool and the Khon Kaen osteoporosis study score for assessing people at risk for osteoporosis are used in planning management [3-5]. The challenge appears when patients do not respond to traditional line of management or have severe osteoporosis at risk of fragility fractures and unable to tolerate conventional agents. The advent of biologic agents has provided a more specific and targeted approach to the treatment of osteoporosis.

ROMOSOZUMAB

Mechanism of Action

Sclerostin is a glycoprotein secreted by osteocytes has been acknowledged found to play a critical role in bone metabolism by inhibiting activation of osteoblast function and bone formation. It inhibits Wnt signalling in osteoblast lineage cells, leading to decreased bone formation by osteoblasts and increased bone resorption by osteoclasts [6].

The Wnt signalling pathways are a group of signal transduction pathways which begin with proteins that pass signals into a cell through cell surface receptors and affect cell function. Wnt binds to LDL (Low Density Lipoprotein)-Receptor-related Protein (LRP) LRP5 and LRP6 co-receptors and Frizzled family receptor leading to activation of the Wnt signalling pathway in osteoblasts and bone formation. By inhibiting sclerostin, Romosozumab stimulates osteoblastic activity and increases bone formation [7].

Romosozumab is a bone-forming agent and a sclerostin antibody that exerts a dual effect on bone, increasing bone formation by osteoblastic activity and decreasing bone resorption resulting in insignificant improvement in BMD as compared to other available therapies. This dual action of the treatment with romosozumab leads to more pronounced increases in BMD than other treatment modalities and reduces the risk of vertebral and clinical fractures by 73% and 36% compared to placebo after 12 months and the sequential treatment regime [8]. Romosozumab increases bone formation by promoting osteoblast differentiation and activity through conversion of bone lining cells to osteoblasts, osteoblastic differentiation of osteoprogenitor cells, and increased bone matrix production by mature osteoblasts [9]. Romosozumab also decreases bone resorption by altering expression of osteoclast regulators including decreasing osteoclast activators RANK (Receptor Activator of Nuclear factor Kappa-B Ligand) and Colony Stimulating Factor-1 (CSF-1) and increasing osteoclast inhibitors OPG (Osteoprotegerin) and WISP (Wnt-1-Induced Secreted Protein-1) [10]. Romosozumab thus is involved in increasing bone formation and decreasing bone resorption.

Romosozumab has been granted marketing authorization by major regulatory authorities in the world including Japan, approved by the Food and Drug Administration (FDA) the USA, Korea, Canada, Australia, and the European Union [11]. It has recently been approved by the National Institute for Care and Health Excellence (United Kingdom) in patients with severe osteoporosis postmenopausal women at increased risk of fractures [12].

In India, recently the Central Drugs Standard Control Organisation, Expert Committee have recommended for grant of permission for import and marketing of romosozumab in the treatment of postmenopausal women with osteoporosis who are at a high

risk for fracture. This is defined as a patient with a history of osteoporotic fracture, or having multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy [13].

Dosages

Romosozumab injection is available in solution form for subcutaneous injection supplied in a single use prefilled syringe which delivers 1.17 mL of a solution containing 105 mg of romosozumab. For an adult, 210 mg once a month for 12 months, supplement with calcium and vitamin D, it is to be administered as two consecutive 105 mg injections at different injection sites into the thigh, abdomen or upper arm [14]. This is to ensure adequate levels of calcium and vitamin D whilst undergoing treatment with romosozumab. It is advisable to correct hypocalcaemia before therapy is initiated. Monitoring for signs and symptoms of hypocalcaemia during therapy is essential [14].

Handling and Storage

It is advised to store romosozumab in a refrigerator between 2-8°C and protect it from light [12].

Therapeutic Uses

Romosozumab is predominantly recommended in postmenopausal women with severe osteoporosis and at increased risk of fractures [12]. Recent guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinology have given a route map of when romosozumab can be used [15]. Romosozumab, which has anabolic effect with monoclonal antibody properties has a significant role in high-risk patients with osteoporosis [16]. Romosozumab has found to be superior to alendronic acid and placebo combination in reducing the incidence of vertebral fractures [17]. The beneficial effect of Romosozumab declines after 12 monthly doses, so its duration of use should be limited to 12 months. For further treatment, antiresorptive agents should be considered. A zoledronate follow-on regimen can maintain robust BMD gains achieved with romosozumab treatment [18]. Romosozumab for 12 months followed by alendronate reduced the risk of vertebral, non vertebral, and hip fractures by 48%, 20% and 38%, respectively compared to alendronate after 2-3 years [8]. Romosozumab also has a crucial role in patients with severe, refractory osteoporosis who have already tried Teriparatide for 18 months. This drug has an advantage over Teriparatide in that Romosozumab can be used in postmenopausal osteoporosis patients who had previous radiation exposure [19].

Side-effects [14]

- **Common or quite common:** Arthralgia; headache; hypersensitivity; increased risk of infection; muscle spasms; neck pain; skin reactions.
- **Uncommon:** Cataract; hypocalcaemia; myocardial infarction; stroke.
- **Rare or exceedingly rare:** Angioedema.
- **Frequency not known:** Atypical femur fracture; cardiovascular event; osteonecrosis of jaw.

Precautions

1. **Major Adverse Cardiac Events (MACE):** Romosozumab use was associated with an increased risk of MACE, a composite of total mortality, myocardial infarction, cerebrovascular disease, and heart failure-related hospitalisation, when compared to alendronate treatment [20]. When compared to alendronate medication, rosozumab use was associated with an elevated risk of MACE, an aggregate of mortality risk, myocardial infarction, stroke, and heart failure-related hospitalisation [20]. Those who suffered a heart attack or cerebrovascular event 12 months before should not be started on romosozumab. If a patient has a heart attack or a cerebrovascular disease while on romosozumab, the medication should be stopped. In a patient with history of myocardial infarction and ischaemic stroke, romosozumab should be used judiciously. The cause of the cardiovascular effect is due to its role in arterial calcification due to increased Sclerostin expression in smooth muscle tissue in areas of vascular calcification [21].
2. **Osteonecrosis of the jaw:** Osteonecrosis of the Jaw (ONJ) has been reported in patients receiving romosozumab [12]. A routine oral and dental examination is required prior to the initiation of romosozumab treatment.
3. **Atypical Femoral Fractures (AFF):** Atypical femoral fractures were described in patients receiving romosozumab just like they have in those taking other bisphosphonates [22]. It is important to rule out the possibility of an incomplete fracture due to an atypical fracture in any patient who complains of pain in their thighs. When a patient develops an atypical femoral fracture, they must be screened for signs and symptoms of femoral fracture in the contralateral leg. Patients should report new or unusual discomfort in the groin, hip, and thigh during treatment [23]. Consideration should be given to stopping romosozumab treatment depending on benefit-risk analysis [24].

Contraindications to Romosozumab Use

- **Hypocalcaemia:** Romosozumab is contraindicated in patients with hypocalcaemia. It should be corrected prior to initiating treatment with romosozumab. Patients should be monitored for signs and symptoms of hypocalcaemia. Patients should be adequately supplemented with calcium and vitamin D while on romosozumab [25].
- **History of myocardial infarction or stroke:** It is advisable to discontinue romosozumab if myocardial infarction or stroke occurs during treatment [26].
- **Systemic hypersensitivity:** Any patient who has had an adverse reaction to romosuzumab in the past, whether it was to romosozumab or any of its formulation, should not be treated with it. If the patient experiences an anaphylactic or allergic reaction while taking romosuzumab, the patient should stop taking the drug immediately [27].

Monitoring of Patient Parameters [25]

1. It is advisable to monitor serum calcium concentration in patients with severe renal impairment, or in those receiving dialysis- increased risk of hypocalcaemia.
2. It is advisable to correct hypocalcaemia before therapy is initiated. It is also prudent to monitor for signs and symptoms of hypocalcaemia during therapy.

CONCLUSION(S)

Romosozumab with its unique mechanism of action provides a significant alternative for the treatment of severe osteoporosis. Romosozumab reduces the risk of vertebral and clinical fractures in women with postmenopausal osteoporosis, with a favourable balance of benefits and risks. Romosozumab is a promising emerging anabolic agent based on favourable results from several phase III trials in postmenopausal women with osteoporosis, and a single trial in men with osteoporosis. Romosozumab may thus expand the options for treating osteoporotic patients at high risk of fracture.

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