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Review article

Romosozumab and cardiovascular safety in Japan

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ABSTRACT

Romosozumab is a potent pharmacological tool to prevent fractures in osteoporosis patients, and its mechanism of action is distinct from any other drugs. The efficacy of romosozumab to prevent osteoporotic fractures is remarkable. However, there remains a concern of increased cardiovascular adverse events. Further relevant investigations are essential to understand whether romosozumab is actually involved in the development of cardiovascular events or not. We need more robust evidence to establish an appropriate and reasonable guide to prescribe romosozumab in our clinical practice.

1. Introduction

Osteoporosis is a disorder of increased fracture risk because of low bone mass and impaired bone quality, such as microarchitectural deterioration of the trabecular and cortical bone [1]. Strategies to stimulate new bone formation are necessary for the restoration of the impaired bone architecture. However, until recently, standard treatments for osteoporosis are antiresorptive drugs that decrease bone resorption and bone formation so that their ability to restore skeletal architecture is limited [2]. Intermittent subcutaneous injections of teriparatide, a fragment of parathyroid hormone, and abaloparatide, a parathyroid hormone-related protein analog, increase bone formation [2]. They also activate bone resorption [2], although once a week teriparatide is less potent to stimulate bone resorption [3]. Thus, their anabolic actions to improve deteriorated skeletal architecture are derived from their activation of bone remodeling and are dependent on the balance of bone formation and resorption [2]. They may not sometimes work to restore the disconnected architecture of trabecular bone. Therefore, we need an option to improve bone architecture by simply building bone matrices when we face patients with highly destructed bone structures. Recently, a humanized antibody against sclerostin, romosozumab, has been approved as an anti-osteoporosis drug that stimulates bone formation but inhibits resorption [4]. This dual action anabolic agent has been clinically available since early 2019 in Japan and sometime later in some other countries. Before its launch, cardiovascular safety concerns of romosozumab indicated in the report of the ARCH (Active-contRolled fraCture study in postmenopausal women with osteoporosis at High risk of fracture) study [5] were clinically disturbing. This issue remains to be addressed during daily clinical use once after romosozumab is available.

This article will briefly review concerns about cardiovascular safety in romosozumab obtained from prospective randomized control trials and present real-world clinical data for its safety, especially in Japan.

2. Sclerostin in the skeletal system

Sclerostin is a pivotal inhibitor of bone formation and has been discovered by some groups investigating patients with 2 rare autosomal recessive syndromes associated with high bone mass [6]. Sclerosteosis is a hereditary disorder characterized by a high bone mass due to inactivating mutations of the SOST gene encoding sclerostin. Excess bone growth during childhood results in skull deformity, cranial and basilar stenosis, cranial nerve compression, and mandibular hypertrophy. A noncoding deletion of a gene essential for transcription of the SOST gene causes Van Buchem disease, another congenital disorder of bone metabolism similar to

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sclerosteosis. Heterozygous siblings of both diseases have a higher bone mineral density (BMD) than healthy controls, without other clinical features. So far, higher cardiovascular incidence in family members of sclerosteosis and Van Buchem disease has not been observed, and cardiovascular risks have not been identified in them.

3. Cardiovascular safety in romosozumab

Cardiovascular safety concerns of romosozumab were first indicated in the report of the ARCH study [5]. Enrolled patients in the ARCH study were older and had clinical features indicating higher cardiovascular risk than those in prior clinical studies of romosozumab. Differences in overall adverse events and serious adverse events were not observed between the romosozumab and the alendronate groups in the ARCH. However, adjudicated serious cardiovascular adverse events were identified more frequently in the romosozumab group than in the alendronate group during the first year (2.5% vs 1.9%) [5]. In contrast, such a difference was not reported in the FRAME (FRActure study in postmenopausal woMen with ostEoporosis) study [7].

Potential mechanisms related to cardiovascular adverse events caused by romosozumab are yet unclear [8]. There is no reasonable explanation for the discrepancy between the FRAME and ARCH studies at this moment. It has been reported that sclerostin may have positive, negative, or no effect on arterial calcification [9]. Sclerostin is most highly expressed in osteocytes, although its expression is also observed in some other tissues. The binding of sclerostin to low-density lipoprotein receptor-related proteins (LRPs) 5 and 6 impairs triggering canonical Wnt signaling in the bone to decrease bone formation. Interestingly, patients with impaired LRP6 functions disrupting Wnt signaling have low bone mineral density and are susceptible to ischemic heart diseases early in their lives [10]. Based on these findings, one can speculate that activating Wnt signaling through neutralization of sclerostin has some benefits against ischemic heart diseases. In contrast, Bovijn J et al [11] reported that the SOST genetic variants were associated with lower risk of fracture and osteoporosis and with a higher risk of myocardial infarction and/or coronary revascularization and major adverse cardiovascular events. The same variants were also associated with increased risk of type 2 diabetes mellitus and higher systolic blood pressure and central adiposity. Together, they suggested that inhibition of sclerostin may elevate cardiovascular risk, warranting a rigorous evaluation of the cardiovascular safety of romosozumab. At this moment, however, there are several controversies in cardiovascular safety in treatment with romosozumab. For example, a study of similar design to the above study recently reported that genetic variants associated with lifelong reduced sclerostin expression were explored for associations with phenotypes including those related to bone physiology and cardiovascular risk factors/events in a population-based phenome-wide association study. The authors concluded that natural genetic modulation of sclerostin by variants with a significant positive effect on bone physiology showed no association with lifetime risk of myocardial infarction or stroke [12].

It is interesting to note that some observational studies suggest that bisphosphonates such as alendronate have protective effects on the development of cardiovascular events [13,14]. However, the cardiovascular benefits of bisphosphonate therapy are not robust or consistent. For example, it has been reported that an analysis of 2 large, long-term, prospective databases in the United States (US) demonstrates no statistically significant differences in the long-term rates of myocardial infarction or death between bisphosphonate users and non-users [15]. The possible cardioprotective effects of bisphosphonates remain inconclusive. In addition, a recent meta-analysis documented that overall mortality was not decreased by bisphosphonate treatment [16]. Therefore, current evidence is not robust enough to recommend using them to treat osteoporosis in those at high risk of cardiovascular diseases, such as myocardial infarction and stroke.

4. Cardiovascular concerns of romosozumab in Japan

Romosozumab was approved in January 2019 in Japan for patients who have osteoporosis with high fracture risk. It has been clinically available since March 2019, the earliest in the world. The osteoporotic patients with high fracture risk were defined to have one of the following four criteria in Japan: (1) BMD T-score ≤ -2.5 and one or more fragility fractures, (2) BMD T-score < -3.3, (3) two or more prevalent vertebral fractures, (4) at least one grade 3 vertebral fracture [17]. A warning was issued in Japan and other countries to physicians who consider the prescription of romosozumab because there was the imbalance in the incidence of MACE (major adverse cardiovascular events) between patients taking romosozumab and alendronate in the ARCH study [5]. The warning is as follows; when romosozumab is an option to treat patients with osteoporosis at high fracture risk, the benefit of fracture prevention versus the risk of cardiovascular events should be fully considered; romosozumab should not be used in patients who experienced ischemic heart disease or cerebrovascular accidents within a year. It is essentially the same as a boxed warning issued by the Food and Drug Administration in the US.

A safety report since the launch of romosozumab in Japan was issued on May 28, 2020 [18]. The report covers safety concerns after prescribing romosozumab from March 4, 2019 to March 7, 2020. The report showed that, out of the overall exposure to romosozumab of 39 352 person-years, the incidence of cerebral strokes was 0.16/100 person-years, and that of ischemic cardiovascular diseases was 0.10/100 person-years (Table 1). Data were recently updated to show that the incidence of cerebral strokes and ischemic cardiovascular diseases in the second year was similar to that of the first year (unpublished observations). These numbers are smaller than the reported incidences in Japan in the general population of cerebral strokes in the Shiga Cohort study (0.40/100 person-years) [19] and cardiovascular accidents in Takashima AMI Registry in Shiga Prefecture (0.17/100 person-years) [20] (Table 1). Those data suggest that so far, romosozumab has been prescribed to appropriate patients to avoid excessive cardiovascular and cerebrovascular risk in Japan. However, it is essential to note that the level of completeness of the information provided may be less than those of cohort studies as described above because pharmacovigilance data of romosozumab in Japan were generated through passive (voluntary) surveillance. Nonetheless, from the data mentioned above, it is reasonable to assume that if romosozumab is prohibited from administrating to patients who correspond to the above-boxed warnings, the risk of cardiovascular and cerebrovascular accidents may be appropriately managed.

Another safety report was published where all cases reported between January 2019 and December 2020 were extracted from the Food and Drug Administration Adverse Event Reporting System

Table 1
Cardiovascular safety of romosozumab report compared to Shiga Cohort Study in Japan.

	Stroke	ICD
Romosozumab [18]	0.164	0.1007
Shiga Cohort [19,20]	0.40	0.17

Incidence with 100 person-years reported on reference numbers of 18, 19, and 20.
ICD, ischemic cardiovascular diseases.

(FAERS) and analyzed to assess the cardiovascular safety profile of romosozumab in the extensive pharmacovigilance database [21]. In that report, the outcome of interest was MACE (myocardial infarction, stroke, or cardiovascular death). Investigators conducted a disproportionality analysis by estimating the reporting odds ratios (RORs) and 95% confidence intervals. Most of the eligible cases with romosozumab were reported from Japan (n = 1188; 59.5%) and US (n = 787; 39.4%). Among them, 206 reports of suspected MACE were identified, and again most cases were from Japan (n = 164; 13.8%) and the US (n = 41; 5.2%). ROR of MACE was elevated in general (4.07; 95% CI, 2.39–6.93). ROR of MACE in Japan (3.56; 95% CI, 1.98–6.38) was higher than the US (1.83; 95% CI, 0.84–4.00). The ROR is primarily dependent on the significant disproportionality observations in the Japanese reports. Patients were older and more frequently male in the Japanese reports than those from the US. All cases with a MACE were older and took more frequently cardioprotective drugs than those without cardiovascular events. Because elderly patients are more prone to cardiovascular and cerebrovascular diseases and because cardiovascular death is more common in men than in women, it is possible to speculate that disproportion in reports for MACE between Japanese and the US is dependent on more reports in older, male, or cardioprotective drugs taking patients from Japan than the US. Pharmacovigilance studies to identify a potential signal for elevated MACE are yet inconclusive.

Much more real-world evidence should be generated to account for sources of bias and confounding in reports of patients with cardiovascular events during the treatment with romosozumab. Until we can reach definite conclusions on the issue of cardiovascular safety of romosozumab, data so far available support the restricted prescribing recommendations in the boxed warnings that patients at a high risk of cardiovascular disease and stroke should not be considered for treatment with romosozumab.

Conflicts of interest

Yasuhiro Takeuchi has disclosed that he received research grants from Chugai Pharmaceutical Co., Ltd., Japan, Teijin Pharma Ltd., Japan, and Daiichi-Sankyo Inc., Japan, and is a member of the speakers' bureau for Chugai Pharmaceutical Co., Ltd., Japan, Daiichi-Sankyo Inc., Japan, Teijin Pharma Ltd., Japan, Amgen Inc., US, Astellas Pharma Inc., Japan, and Asahi Kasei Pharma Corp., Japan.

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