LETTER TO THE EDITOR

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# Serious Adverse Events With Romosozumab Use in Japanese Patients: Need for Clear Formulation of Contraindications Worldwide

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**To the Editor**

Romosozumab (commercial name: Evenity), a bone-forming monoclonal antibody that is designed to work by inhibiting the activity of sclerostin, has been developed for the treatment of osteoporosis by Amgen Inc. (Thousand Oaks, CA, USA). However, it is an anomaly that Japan is the first country in the world where romosozumab was commercially launched, which eventually led to serious problems.

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommended refusal of the marketing authorization in July 2017 and in June 2019, respectively. These decisions were based on the Active-Controlled Fracture Study in Postmenopausal Women With Osteoporosis at High Risk of Fracture (ARCH) study (https://clinicaltrials.gov/ct2/show/NCT01631214),[1] in which romosozumab resulted in a significantly higher incidence of severe cardiovascular (CV) adverse events compared with the active control, alendronate. Similar findings were not reported in the other global phase III studies, Fracture Study in Postmenopausal Women With Osteoporosis (FRAME)[2] and Placebo-Controlled Study Evaluating the Efficacy and Safety of Romosozumab in Treating Men With Osteoporosis (BRIDGE).[3] The application of Astellas-Amgen, a joint venture of Amgen, Inc. and Astellas (Tokyo, Japan), to the Pharmaceuticals and Medical Devices Agency (PMDA) national authority in Japan was based on the subgroup analysis of the FRAME study in the Japanese population.[4] However, Japan did not participate in the ARCH study in question, so there are no data from the subgroup analysis of the Japanese population. As a matter of course, Astellas-Amgen should have conducted an independent study to examine the risk of adverse CV events associated with the usage of this drug in the Japanese population, However, such a nationwide study was not performed at all. Despite the lack of data that may have overridden the recommendation from FDA and EMA, Astellas-Amgen applied for marketing authorization to the PMDA. Surprisingly, PMDA granted approval for this drug in December 2018 without sufficient available evidence, which was a first in the world. Subsequently, romosozumab was launched to the Japanese market in March 2019.

Unfortunately, the postmarketing survey revealed unfavorable results, which added to the apprehension of Japanese physicians and researchers. In July 2019, Astellas-Amgen issued a press release on the adverse effects of the drug, disclosing 11 cases of severe CV adverse events in the first 3 months of commercial availability (March 2019 to June 2019). These included three deaths; one was a 71-year-old man who died on the day after the injection owing to heart failure. Since then, the scenario has worsened considerably, with press releases in October 2019 after 6 months of marketing (March 2019 to September 2019) revealing 68 severe CV events including 16 deaths whose relationship to the drug could not be denied.[5] Thus, 57 severe CV events and 13 deaths occurred in 3 months (June 2019 to September 2019).

Although the FDA finally approved romosozumab in April 2019, approximately 4 months after the PMDA approval, the status in the US is considerably different than that in Japan. FDA clearly states, in a black box warning, on the official prescribing instructions: "Romosozumab should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year."[6] Recently, EMA also recommended approving romosozumab in October 2019, with a strict statement: "Romosozumab should not be used in such women if they have previously had a heart attack (myocardial infarction) or stroke."[7]

In clear contrast, the black box warning of contraindication on the Japanese prescribing instructions issued by Astellas-Amgen does not mention CV events at all, and only states drug allergy and hypocalcemia. Even after the postmarketing survey revealed many unexpected severe CV events in June 2019, the prescribing instruction added an inconspicuous and unspecific red box warning stating that "Judge depending on the benefits and risks. If a patient experiences CV events during therapy, ask patients to consult related doctors."[8] If Astellas-Amgen had included a clear statement in the boxes like the FDA and EMA instructions, a proportion of the severe CV events and deaths that occurred between June 2019 and September 2019 could have been avoided.

Because these are the first real-world data obtained by the postmarketing survey, this is no longer only a national issue. This

Received in original form August 24, 2019; revised form November 6, 2019; accepted December 7, 2019.
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Journal of Bone and Mineral Research, Vol. 00, No. 00, Month 2020, pp 1–2.
DOI: 10.1002/jbmr.4001

information needs to be shared with all the countries in the world in which romosozumab will be used for the treatment of osteoporosis. We should stress here that osteoporosis is not a disease that should lead to the death of 16 patients in 6 months. Indeed, similar immediate postmarketing surveys of the other bone anabolic agents in Japan had reported many fewer deaths in 6 months: only one death with daily teriparatide (commercial name: Forteo) and 2 deaths with once-weekly teriparatide (commercial name: Teribone).

Romosozumab is, undoubtedly, a revolutionary drug for the treatment of osteoporosis. However, it should be appropriately prescribed in accordance with the instructions of the FDA and EMA. Unfortunately, the status was different in Japan. This revolutionary drug needs to be made available to patients with osteoporosis worldwide with clear indication of the contraindications.

## Disclosures

I declare that I have no competing interests.

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