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Summary of Study Results Using National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB)

March 5, 2025

Study title

Evaluation of the risk of cardiovascular events by romosozumab (genetical recombination) using NDB

Products investigated

Romosozumab (genetical recombination) (hereinafter referred to as “romosozumab”)

Background:

- Romosozumab was approved for “osteoporosis with a high risk of fracture” in January 2019 and launched in March 2019 in Japan.
- The labeling of romosozumab included precautions regarding the risk of cardiovascular events at the time of approval. In September 2019, the warning was strengthened with the addition of precautions on cardiovascular events in the warning section and other sections, based on individual case safety reports (ICSRs) on the events and status of related overseas measures[1].
- Despite the accumulation of ICSRs on cardiovascular events after the administration of romosozumab, evaluating the relationship between romosozumab and these events was challenging, as ICSRs alone could not rule out the influence of other

[1] https://www.pmda.go.jp/files/000231403.pdf

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contributing factors.

- Pharmacoepidemiological studies using a global medical information database showed no increased risk of cardiovascular events with romosozumab compared with parathyroid hormone preparations. However, no similar studies has been conducted in Japan before this study.

Purpose of the study

This study aimed to evaluate the relationship between romosozumab and cardiovascular events by comparing the incidence of cardiovascular events between romosozumab and teriparatide treatments[2].

Reason to select NDB for the study and data period

Reason to select: It was selected because it is the nationwide database in Japan, and it is possible to collect medical information from nationwide multiple different medical institutions.

Data period: August 1, 2010 to March 31, 2023

Outline of method

Study population

Patients who were prescribed or dispensed romosozumab or teriparatide between March 4, 2019, and March 31, 2023, were identified. Of these, patients with a first medical claim at least one year or more before t_0, which was defined as the earliest date of prescription or dispensation date, were included in the study population after applying the exclusion criteria[3]. Patients in the study population were assigned to the exposure group if they received

[2] "Teriparatide" included teriparatide acetate, which was osteoporosis drug, and teriparatide (genetical recombination).

[3] i) patients younger than 40 years of age at t_0, ii) patients prescribed or dispensed romosozumab or teriparatide within one year before t_0, iii) patients prescribed or dispensed romosozumab and teriparatide concomitantly at t_0, iv) patients prescribed or dispensed antineoplastic drugs on or before t_0, v) patients with no follow-up period

romosozumab at t_0 and to the control group[4] if they received teriparatide.

■ **Follow-up period**

Start date and end date of follow-up period were defined as follows.

- Start date: The day after the date of t_0
- End date: The earliest date of the following
  - i) Occurrence date of outcome
  - ii) End date of treatment period*
  - iii) Prescription or dispensation date of a drug assigned to a different group (exposure or control)
  - iv) Last date of the month with the last medical claim
  - v) 13 months after t_0

* A consecutive prescription within the same group was considered as a continuous treatment if the gap between the end date† of previous prescription or dispensation and the start date of the subsequent prescription or dispensation was within 30 days. The end date of the treatment period was defined as the end date of the last prescription plus 30 days of treatment.

† The end date of prescription or dispensation was defined as the start date of prescription or dispensation plus the duration (refer to the following table).

Non-proprietary Name	Administration	Duration
Romosozumab (genetical recombination)	Once a month	30 days
Teriparatide (genetical recombination)	Once a day	N × 28 days
Teriparatide acetate	Once a week Twice a week	7 days n / 2 × 7 days

n: the number of prescribed preparations of a drug

[4] Teriparatide was chosen as the control group because it has the same indication as romosozumab and has been used since before launch of romosozumab in Japan. In addition, the labeling of teriparatide does not include precautions on severe cardiovascular events during the data period.

■ Outcome definition

- Outcome:
  Major Adverse Cardiovascular Events (MACE) (composite outcome of acute myocardial infarction[5], acute coronary syndrome[6], cerebral infarction,[7] and cerebral hemorrhage[8])
- Occurrence date of outcome:
  Earliest date of hospitalization that first met the definition of MACE during the follow-up period

■ Analysis methods

- Patient characteristics were tabulated, and the absolute standardized mean difference (ASD) was calculated to confirm differences in patient characteristics. A reference value of 0.1 was used to assess the imbalance in patient characteristics.
- We estimated the crude hazard ratio (cHR) and adjusted hazard ratio (aHR)[9] for MACE with romosozumab compared to teriparatide using the Cox proportional hazards model.
- Subgroup analyses were performed based on the patient's history of MACE (defined as per the outcome definition), and categorized into three groups: none, the one-year period

[5] The hospitalization with a diagnosis code for "acute myocardial infarction" must be recorded, and at least one of "percutaneous coronary intervention," "coronary artery bypass surgery," "intra-aortic balloon pumping," "percutaneous cardiopulmonary support," or "thrombolysis" must be performed within 30 days from the admission date.

[6] The hospitalization with a diagnosis code for "acute coronary syndrome" must be recorded, and at least one of "percutaneous coronary intervention," "coronary artery bypass surgery," "intra-aortic balloon pumping," "percutaneous cardiopulmonary support," or "thrombolysis" must be performed within 30 days from the admission date.

[7] The hospitalization with a diagnosis code for "cerebral hemorrhage" must be recorded. At least one of "computed tomography," "magnetic resonance angiography," or "magnetic resonance computed tomography" must be performed during the period between the day before the admission date and 30 days after the admission date, and at least one of "antiedematous drugs," "antihypertensive drugs (injection)," or "hematoma removal surgery" must be prescribed or performed within 30 days from the admission date.

[8] The hospitalization with a diagnosis code for "cerebral infarction" must be recorded. At least one of "computed tomography," "magnetic resonance angiography," or "magnetic resonance computed tomography" must be performed during the period between the day before the admission date and 30 days after the admission date, and at least one of "cerebroprotective drugs," "antiplatelet drugs (injection)," "anticoagulant drugs (injection)," "thrombolytic drugs," "antiedematous drugs," "craniotomy," or "thrombectomy" must be prescribed or performed within 30 days from the admission date.

[9] Adjustment factors: age categories, sex, disease history (MACE, dyslipidemia, diabetic mellitus, hypertension, heart failure, chronic obstructive pulmonary disease, and chronic renal failure), and prescription history (antiplatelet drugs and anticoagulant drugs)

leading up to t_0 (hereinafter referred to as “recent past”), and more than 1 year before t_0 (excluding the exact date one year before t_0) (hereinafter referred to as “distant past”). This classification aligns with the labeling of romosozumab.

- Subgroup analyses according to sex were performed, because cardiovascular events are generally considered to occur more commonly in male than in female.

Outline of results

■ Patient background

- The number of patients included in the main analysis were 251,219 in the exposure group and 500,445 in the control group. The most frequent 10-year age categories was 80–89 years for both groups, and there was no difference between the groups in terms of the distribution of age categories (see Appendix Table 1).
- There were significant differences between the groups in terms of sex and anticoagulant prescription history. The proportion of male patients was 9.33% in the exposure group and 14.14% in the control group (ASD, 0.15). The proportion of patients with a history of anticoagulant drug prescription was 7.13% in the exposure group and 10.32% in the control group (ASD, 0.11). For the other patient characteristics, ASDs exceeding 0.1 were not observed.

■ Risk assessment

- MACE were observed in 1,853 patients in the exposure group and in 3,427 patients in the control group during the follow-up period. The aHR (95% confidential interval [95% CI]) for MACE was 1.00 (0.94–1.06) (see appendix Table 2-1).
- In the subgroup analysis by a history of MACE, the aHRs (95% CI) for MACE in patients with none, recent past, and distant past, were 1.01 (0.95–1.08), 0.93 (0.72–1.21) and 1.00 (0.85–1.18), respectively (see appendix Table 2-2).
- In the subgroup analysis by sex, the aHRs (95% CI) for MACE were 0.93 (0.81–1.07) for male and 1.02 (0.96–1.09) for female (see appendix Table 2-3).

■ **Discussion based on the results**

- Regarding patient characteristics, no differences were observed in all variables between the groups, except for the proportion of male patients and patients prescribed anticoagulant drugs.
- All results consistently showed that the risk of MACE with romosozumab was not higher than that with teriparatide, regardless of sex or history of MACE.
- It should be noted that there are some limitations in the evaluation of the results, including the following: Although the outcome definition used in this study was set based on previous validation studies using MID-NET®, the validation study in the NDB has been unachievable; there is a certain limit to the reliability of information on exposure and patient traceability; other potential confounders (e.g., smoking, body mass index, lifestyle) may have affected the results.

Appendix

Table 1. Patient characteristics

	Exposure group		Control group		ASD
	n	(%)	n	(%)	
Study patients	251,219	(100.00)	500,445	(100.00)	-
Age categories (years)					
40–49	894	(0.36)	1,989	(0.40)	0.01
50–59	5,143	(2.05)	11,744	(2.35)	0.02
60–69	22,467	(8.94)	49,153	(9.82)	0.03
70–79	85,317	(33.96)	167,886	(33.55)	0.01
80–89	111,302	(44.30)	212,325	(42.43)	0.04
90–99	25,741	(10.25)	56,180	(11.23)	0.03
>100	355	(0.14)	1,168	(0.23)	0.02
Sex					
Male	23,450	(9.33)	70,752	(14.14)	0.15
Disease history					
MACE[10]					
None	238,681	(95.01)	465,872	(93.09)	0.08
Recent past	1,626	(0.65)	6,023	(1.20)	0.06
Distant past	10,912	(4.34)	28,550	(5.70)	0.06
Dyslipidemia	90,686	(36.10)	183,442	(36.66)	0.01
Diabetes mellitus	28,724	(11.43)	68,974	(13.78)	0.07
Hypertension	141,156	(56.19)	292,831	(58.51)	0.05
Heart failure	67,291	(26.79)	154,806	(30.93)	0.09
Chronic obstructive pulmonary disease	4,966	(1.98)	11,615	(2.32)	0.02
Chronic renal failure	16,606	(6.61)	29,411	(5.88)	0.03
Prescription history					
Antiplatelet drugs	31,811	(12.66)	77,612	(15.51)	0.08
Anticoagulant drugs	17,917	(7.13)	51,622	(10.32)	0.11

[10] Defined as per the outcome definition.

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Table 2-1. Relationship between romosozumab and MACE

Group	Number of patients	Follow-up period (100 py)	Number of MACE	Crude incidence (/100 py)	Crude incidence ratio	cHR[11] (95% CI)	aHR[11,12] (95% CI)
Control	500,445	2,810.74	3,427	1.22	reference	reference	reference
Exposure	251,219	1,697.68	1,853	1.09	0.90	0.90 (0.85 – 0.96)	1.00 (0.94 – 1.06)

Abbreviation: cHR, crude hazard ratio; aHR, adjusted hazard ratio; py, person-year

Table 2-2. Subgroup analyses (by a history of MACE) : Relationship between romosozumab and MACE

History of MACE	Group	Number of patients	Follow-up period (100 py)	Number of MACE	Crude incidence (/100 py)	Crude incidence ratio	cHR[11] (95% CI)	aHR[11,13] (95% CI)
None	Control	465,872	2,634.62	2,696	1.02	reference	reference	reference
	Exposure	238,681	1,620.19	1,565	0.97	0.94	0.95 (0.89 – 1.01)	1.01 (0.95 – 1.08)
Recent past	Control	6,023	28.97	258	8.90	reference	reference	reference
	Exposure	1,626	9.15	71	7.76	0.87	0.92 (0.71 – 1.20)	0.93 (0.72 – 1.21)
Distant past	Control	28,550	147.15	473	3.21	reference	reference	reference
	Exposure	10,912	68.34	217	3.18	0.99	0.99 (0.84 – 1.16)	1.00 (0.85 – 1.18)

Table 2-3. Subgroup analyses (by sex) : Relationship between romosozumab and MACE

Sex	Group	Number of patients	Follow-up period (100 py)	Number of MACE	Crude incidence (/100 py)	Crude incidence ratio	cHR[11] (95% CI)	aHR[11,14] (95% CI)
Male	Control	70,752	365.86	758	2.07	reference	reference	reference
	Exposure	23,450	142.45	258	1.81	0.87	0.88 (0.77 – 1.02)	0.93 (0.81 – 1.07)
Female	Control	429,693	2,444.88	2,669	1.09	reference	reference	reference
	Exposure	227,769	1,555.22	1,595	1.03	0.94	0.95 (0.89 – 1.01)	1.02 (0.96 – 1.09)

[11] Hazard ratio was estimated using the Cox proportional hazards model.
[12] aHR was estimated to adjust for age categories, sex, disease history (MACE, dyslipidemia, diabetes mellitus, hypertension, heart failure, chronic obstructive pulmonary disease, chronic renal failure), and prescription history (antiplatelet drugs and anticoagulant drugs)
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