Association between use of romosozumab and cardiovascular events: analysis of the Japanese Adverse Event Report database

Kazumasa Kotake[1], Satoru Mitsuboshi[2], Yuki Omori[1], Yukio Kawakami[1], and Yasuhiro Kawakami[1]

[1]Okayama Saiseikai General Hospital
[2]Kaetsu Hospital

March 07, 2024

Abstract

There is concern about an increased risk of cardiovascular events in romosozumab users. This study evaluated the association between use of romosozumab and cardiovascular events using the Japanese Adverse Drug Event Report database. In total, 868 romosozumab users were identified. Disproportionality of cardiac events (reporting odds ratio [ROR]: 11.5, 95% confidence interval [CI]: 8.58–15.2; P < 0.01) and cerebrovascular events (ROR: 7.03, 95% CI: 5.46–8.93; P < 0.01) was observed. Cardiac events were significantly increased in patients with cardiac disease (odds ratio [OR]: 2.74, 95% CI: 1.37–5.49; P < 0.01), hypertension (OR: 1.97, 95% CI: 1.07–3.63; P = 0.03), and diabetes (OR: 2.36, 95% CI: 1.16–4.80; P = 0.02). Similar results were found regarding the risk factors for cerebrovascular events. This study suggests that comorbidities such as hypertension and diabetes may increase the risk of cardiovascular events in romosozumab users.

Introduction

Osteoporosis is a public health problem associated with risk fractures, and this risk has been increasing with aging.[1]Approximately 50% of women and 20% of men over the age of 50 years sustain an osteoporotic fracture, which can lead to long-term pain and disability,[2] and even to death.[1]Hence, drug therapy for osteoporosis is important to improve quality of life and prognosis.

Romosozumab is approved for use in patients with moderate to severe osteoporosis. This drug has the dual effect to stimulate bone formation and inhibit bone resorption by inhibiting sclerostin, an osteocyte protein.[3] Because of its dual effect, the risk of clinical fracture has been found to be 27% lower in patients on romosozumab than in those on oral alendronate.[4]However, romosozumab may increase the risk of cardiovascular events. A randomized controlled trial demonstrated that serious cardiovascular events occurred more frequently in romosozumab users (2.5%) than in alendronate users (1.9%).[4] However, bisphosphonates can reduce arterial wall calcification,[5] and have been associated with decreased risk of cardiovascular events compared with placebo.[6] Therefore, it is unclear whether romosozumab itself increase the risk of cardiovascular events. Identification of risk factors for cardiovascular events may be useful to avoid adverse events with romosozumab and provide appropriate osteoporosis treatments. Herein, we evaluated the association between use of romosozumab and cardiovascular events using the Japanese Adverse Drug Event Report (JADER) database.

Methods

Data source

The JADER database is a spontaneous reporting system for drug-related adverse events in Japan and is managed by the Pharmaceuticals and Medical Devices Agency, which is the Japanese regulatory authority.

This reporting system enables detection of infrequent drug-related adverse events and includes four categories: "DEMO" for patient demographic information, "DRUG" for drug information, "REAC" for adverse events, and "HIST" for primary disease. DRUG includes three categories of adverse events: "suspected drug," "concomitant drug," and "interacting drug."

Data collection

Institutional review board approval was not required for this observational study using anonymized patient data in the JADER database, which is freely available to the public. Data recorded from April 2004 to May 2021 were downloaded from the Pharmaceuticals and Medical Devices Agency website (*http://www.pmda.go.jp/*) on October 3, 2021. Two authors (K.K. and S.M.) independently collected and collated the data.

Definitions

Romosozumab, bisphosphonates, teriparatide, and denosumab, which widely used to treat osteoporosis, were investigated regardless of whether the data reporter suspected possible adverse events. Bisphosphonates were defined as alendronate, etidronate, ibandronate, minodronate, and risedronate: only oral bisphosphonate users were included based on earlier studies.[4,6] The patient selection process is shown in Fig 1.

Cardiac and cerebrovascular events were evaluated. Cardiac events were defined by the Preferred Terms "myocardial infraction," and/or "angina pectoris," and cerebrovascular events by the Preferred Term "cerebral infarction," in REAC. Data on sex, age, and presence of cardiac disease, cerebrovascular disease, hypertension, and diabetes were collected from DEMO. Cardiac disease was defined as identified comorbidities, including the reported Preferred Terms "heart failure," and/or "angina pectoris," and/or "atrial fibrillation," in HIST. These comorbidities have been reported to be associated with development of cardiac disease.[7-9] Cerebrovascular disease was defined as identified comorbidities, including the reported Preferred Terms "cerebral infarction," in HIST. Hypertension and diabetes were defined as identified comorbidities, including "hypertension" and/or "diabetes," in HIST respectively. Duplicate reports from patients with non-oral bisphosphonate users and concomitant use of osteoporosis drugs and were excluded.

Statistical analysis

The frequency of cardiovascular events according to type of osteoporosis drug was compared using Fisher's exact test. The reporting odds ratio (ROR), which can identify drug-associated adverse events, 95% confidence interval (CI), and P-values were calculated. Multivariate logistic analysis was then used to identify cardiac events and cerebrovascular events in romosozumab users. Sex, age [?]80 years, and presence of cardiac disease, cerebrovascular disease, hypertension, and diabetes were included in the analysis. Modelling was based on a complete-case analysis. Odds ratio (OR), 95% CI, and P-values were calculated. All analyses were performed using R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria). A P-value < 0.05 was considered statistically significant.

Results

We identified 705,924 reports, of which 702,072 were applicable excluding non-oral bisphosphonate users and concomitant use of other osteoporosis drugs. As shown in Table 1, disproportionality for cardiac events was observed in romosozumab users (ROR: 11.5, 95% CI: 8.58–15.2; $P < 0.01$) and teriparatide users (ROR: 1.82, 95% CI: 1.22–2.63; $P < 0.01$). Disproportionality for cerebrovascular events was observed in only romosozumab users (ROR: 7.03, 95% CI: 5.46–8.93; $P < 0.01$).

Table 2 shows that the risk of cardiac events was significantly increased in the presence of cardiac disease (OR: 2.74, 95% CI: 1.37–5.49; $P < 0.01$), hypertension (OR: 1.97, 95% CI: 1.07–3.63; $P = 0.03$), and diabetes (OR: 2.36, 95% CI: 1.16–4.80; $P = 0.02$). The risk of cerebrovascular events was significantly increased in the presence of cerebrovascular disease (OR: 4.76, 95% CI: 1.97–11.5; $P < 0.01$), and hypertension (OR: 2.53, 95% CI: 1.49–4.31; $P < 0.01$).

Discussion

The results suggest that disproportionality for both cardiac events and cerebrovascular events was shown in only romosozumab users, and romosozumab may be associated with the risk of cardiac and cerebrovascular events. This result supports previous reports that cardiovascular events are more frequent with romosozumab.[4,10] In fact, the association between use of romosozumab and cardiovascular events may be considered from the mechanism of action of romosozumab. Sclerostin, the site of action of romosozumab, is expressed not only in osteocytes but also in vascular smooth muscle. Therefore, romosozumab specifically binds to sclerostin and inhibits its signalling, and is pointed out to promote vascular calcification.[11]

The results of our study also suggest that comorbidity of hypertension or diabetes may increase cardiac and cerebrovascular events in romosozumab users. These conditions are well-known cardiovascular risk factors, and may further increase the risk of cardiovascular events in romosozumab users.[12] The frequency of cerebrovascular events in romosozumab users was increased only in the presence of hypertension, possibly because the association of cerebrovascular events with hypertension is stronger than that with diabetes.[13] Blood sclerostin levels are known to be increased in patients with hypertension or diabetes.[14,15] Therefore, further research on sclerostin may be key to understanding the association between romosozumab and comorbidity.

Disproportionality for cardiac events was also observed in teriparatide users. It has been reported that teriparatide can cause a transient increase in heart rate but that the risk of major cardiac events is similar to that with placebo.[16] However, teriparatide is widely used in patients with moderate to severe osteoporosis,[17] who are already at higher risk of cardiac events.[18] This might explain why the risk of cardiac events is higher in teriparatide users than in users of other osteoporosis drugs.

This study has four notable limitations. First, romosozumab was launched in March 2019 and its association with serious cardiovascular events was reported in September 2019.[19] We investigated this study until May 2021 and collected romosozumab reports for three years. Because there is a correlation between awareness and number of reports,[20] this report may improve education about cardiovascular events and increase reports of cardiovascular events with romosozumab. Second, romosozumab and teriparatide are used in patients with moderate to severe osteoporosis, who are already at higher risk of cardiac events,[17] so the disproportionality in cardiac events may have been influenced by patient background factors. Third, although some confounding factors, including cardiovascular disease, hypertension and diabetes are adjusted for as much as possible in the JADER database, those related to cardiovascular events, such as abnormal cholesterol levels and smoking, cannot be adjusted for because of the limited search capability of JADER. Finally, we could not assess concomitant medications or the timing of events because of limitations in the dataset and missing data.

This study suggests that romosozumab may be associated with the risk of cardiac and cerebrovascular events, and comorbidities such as hypertension and diabetes may increase the risk of cardiovascular events in romosozumab users. Further study may be needed to clarify the association between the use of romosozumab and cardiovascular events.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Funding

No funding was received for this research.

Data Availability Statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request (kottanketty@gmail.com).

Reference

1. Compston JE, McClung MR, Leslie WD. Osteoporosis. *Lancet* . 2019;393(10169):364-376. doi:10.1016/S0140-6736(18)32112-3

2. Adachi JD, Ioannidis G, Pickard L, et al. The association between osteoporotic fractures and health-related quality of life as measured by the Health Utilities Index in the Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int* . 2003;14(11):895-904. doi:10.1007/s00198-003-1483-3

3. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med* . 2014;370(5):412-420. doi:10.1056/NEJMoa1305224

4. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. *N Engl J Med* . 2017;377(15):1417-1427. doi:10.1056/NEJMoa1708322

5. Kranenburg G, Bartstra JW, Weijmans M, et al. Bisphosphonates for cardiovascular risk reduction: A systematic review and meta-analysis.*Atherosclerosis* . 2016;252:106-115. doi:10.1016/j.atherosclerosis.2016.06.039

6. Kang JH, Keller JJ, Lin HC. Bisphosphonates reduced the risk of acute myocardial infarction: a 2-year follow-up study. *Osteoporos Int* . 2013;24(1):271-277. doi:10.1007/s00198-012-2213-5

7. Metra M, Teerlink JR. Heart failure. *Lancet* . 2017;390(10106):1981-1995. doi:10.1016/S0140-6736(17)31071-1

8. Choi BG, Rha SW, Yoon SG, Choi CU, Lee MW, Kim SW. Association of major adverse cardiac events up to 5 years in patients with chest pain without significant coronary artery disease in the Korean population.*J Am Heart Assoc* . 2019;8(12):e010541. doi:10.1161/JAHA.118.010541

9. Emdin CA, Wong CX, Hsiao AJ, et al. Atrial fibrillation as risk factor for cardiovascular disease and death in women compared with men: systematic review and meta-analysis of cohort studies. *BMJ* . 2016;352:h7013. doi:10.1136/bmj.h7013

10. Lewiecki EM, Blicharski T, Goemaere S, et al. A phase III randomized placebo-controlled trial to evaluate efficacy and safety of romosozumab in men with osteoporosis. *J Clin Endocrinol Metab* . 2018;103(9):3183-3193. doi:10.1210/jc.2017-02163

11. Brandenburg VM, Verhulst A, Babler A, D'Haese PC, Evenepoel P, Kaesler N. Sclerostin in chronic kidney disease-mineral bone disorder think first before you block it! *Nephrol Dial Transplant* . 2019;34(3):408-414. doi:10.1093/ndt/gfy129

12. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension* . 2001;37(4):1053-1059. doi:10.1161/01.hyp.37.4.1053

13. Hu G, Sarti C, Jousilahti P, et al. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. *Stroke* . 2005;36(12):2538-2543. doi:10.1161/01.STR.0000190894.30964.75

14. Gennari L, Merlotti D, Valenti R, et al. Circulating sclerostin levels and bone turnover in type 1 and type 2 diabetes. *J Clin Endocrinol Metab* . 2012;97(5):1737-1744. doi:10.1210/jc.2011-2958

15. Chang YC, Hsu BG, Liou HH, Lee CJ, Wang JH. Serum levels of sclerostin as a potential biomarker in central arterial stiffness among hypertensive patients. *BMC Cardiovasc Disord* . 2018;18(1):214. doi:10.1186/s12872-018-0955-5

16. Cosman F, Peterson LR, Towler DA, Mitlak B, Wang Y, Cummings SR. Cardiovascular safety of abaloparatide in postmenopausal women with osteoporosis: analysis from the ACTIVE phase 3 trial. *J Clin Endocrinol Metab* . 2020;105(11):dgaa450. doi:10.1210/clinem/dgaa450

17. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice guidelines for the diagnosis and treatment of postmenopausal

osteoporosis–2020 update. *Endocr Pract* . 2020;26(Suppl 1):1-46. doi:10.4158/GL-2020-0524SUPPL

18. Qu X, Huang X, Jin F, et al. Bone mineral density and all-cause, cardiovascular and stroke mortality: a meta-analysis of prospective cohort studies. *Int J Cardiol* . 2013;166(2):385-393. doi:10.1016/j.ijcard.2011.10.114

19. Tanaka M, Idei M, Sakaguchi H, et al. Rationales of delay and difference in regulatory review by Japan, the USA and Europe among new drugs first approved in Japan. *Br J Clin Pharmacol* . 2021;87(8):3279-3291. doi:10.1111/bcp.14749

20. Figueiras A, Herdeiro MT, Polónia J, Gestal-Otero JJ. An educational intervention to improve physician reporting of adverse drug reactions: a cluster-randomized controlled trial. *JAMA* . 2006;296(9):1086-1093. doi:10.1001/jama.296.9.1086

Table 1 Proportions of cardiovascular events in patients using osteoporosis drugs

	Onset of cardiac events / Total, n (%)	Reporting odds ratio (95% confidence interval)	P-value*
Non-use of romosozumab	4,097 / 701,204 (0.6)	11.5 (8.58–15.2)	<0.01
Use of romosozumab	55 / 868 (6.3)		
Non-use of oral bisphosphonate	4,064 / 685,957 (0.6)	0.94 (0.76–1.16)	0.64
Use of oral bisphosphonate	90 / 16,115 (0.6)		
Non-use of teriparatide	4,125 / 699,359 (0.6)	1.82 (1.22–2.63)	<0.01
Use of teriparatide	29 / 2,713 (1.1)		
Non-use of denosumab	4,140 / 697,883 (0.6)	0.56 (0.31–0.94)	0.03
Use of denosumab	14 / 4,189 (0.3)		
	Onset of cerebrovascular events / Total, n (%)	Reporting odds ratio (95% confidence interval)	P-value*
Non-use of romosozumab	9,176 / 701,204 (1.3)	7.03 (5.46–8.93)	<0.01
Use of romosozumab	74 / 868 (8.5)		
Non-use of oral bisphosphonate	9,130 / 685,957 (1.3)	0.56 (0.46–0.67)	<0.01
Use of oral bisphosphonate	120 / 16,115 (0.7)		
Non-use of teriparatide	9,217 / 699,359 (1.3)	0.92 (0.63–1.30)	0.74
Use of teriparatide	33 / 2,713 (1.2)		
Non-use of denosumab	9,233 / 697,883 (1.3)	0.30 (0.18–0.49)	<0.01
Use of denosumab	17 / 4,189 (0.4)		

* Fisher's exact test.

A P-value < 0.05 was considered statistically significant.

Table 2 Multivariate logistic analysis of potential risk factors for cardiovascular events in romosozumab users

	Cardiac events / Total, n (%)	Odds Ratio (95% confidence interval)	Odds Ratio (95% confidence interval)	P-value*
		Crude	Adjusted	

	Cardiac events / Total, n (%)	Odds Ratio (95% confidence interval)	Odds Ratio (95% confidence interval)	P-value*
Male sex	11/128 (8.6)	1 [Reference]	1 [Reference]	
Female sex	44/705 (6.2)	0.59 (0.32–1.09)	0.72 (0.38–1.38)	0.33
Not reported sex	0/35 (0)	NA	NA	NA
Age < 80 years	24/328 (7.3)	1 [Reference]	1 [Reference]	
Age [?] 80 years	26/426 (6.1)	0.79 (0.52–1.19)	0.79 (0.49–1.27)	0.33
Not reported age	5/114 (4.4)	0.78 (0.44–1.34)	0.67 (0.38–1.20)	0.18
Without cardiac disease	41/786 (5.2)	1 [Reference]	1 [Reference]	
With cardiac disease	14/82 (17)	3.74 (1.94–7.21)	2.74 (1.37–5.49)	<0.01
Without cerebrovascular disease	52/842 (6.2)	1 [Reference]	1 [Reference]	
With cerebrovascular disease	3/26 (12)	1.98 (0.58–6.82)	1.05 (0.28–3.96)	0.95
Without hypertension	29/650 (4.5)	1 [Reference]	1 [Reference]	
With hypertension	26/218 (12)	2.90 (1.67–5.04)	1.97 (1.07–3.63)	0.03
Without diabetes	40/784 (5.1)	1 [Reference]	1 [Reference]	
With diabetes	15/84 (18)	4.04 (2.13–7.69)	2.36 (1.16–4.80)	0.02
	Cerebrovascular events / Total, n (%)	Odds Ratio (95% confidence interval) Crude	Odds Ratio (95% confidence interval) Adjusted	P-value*
Male sex	7/128 (5.5)	1 [Reference]	1 [Reference]	
Female sex	64/705 (9.1)	1.41 (0.78–2.54)	1.64 (0.86–3.14)	0.13
Not reported sex	3/35 (8.6)	1.29 (0.88–1.90)	1.27 (0.86–1.87)	0.70
Age < 80 years	25/328 (7.6)	1 [Reference]	1 [Reference]	
Age [?] 80 years	45/426 (11)	0.91 (0.64–1.31)	0.90 (0.61–1.33)	0.59
Not reported age	4/114 (3.5)	1.21 (0.73–2.00)	1.07 (0.63–1.80)	0.80
Without cardiac disease	63/786 (8.0)	1 [Reference]	1 [Reference]	
With cardiac disease	11/82 (13)	1.78 (0.90–3.53)	1.51 (0.72–3.18)	0.27
Without cerebrovascular disease	65/842 (7.7)	1 [Reference]	1 [Reference]	
With cerebrovascular disease	9/26 (35)	6.33 (2.71–14.8)	4.76 (1.97–11.5)	<0.01
Without hypertension	41/650 (6.3)	1 [Reference]	1 [Reference]	
With hypertension	33/218 (15)	2.65 (1.63–4.31)	2.53 (1.49–4.31)	<0.01
Without diabetes	67/784 (8.5)	1 [Reference]	1 [Reference]	
With diabetes	7/84 (8.3)	0.97 (0.43–2.19)	0.53 (0.22–1.32)	0.17

*Multivariate logistic regression analysis.

A P-value < 0.05 was considered statistically significant.

Modeling was based on a complete case analysis.

NA, not applicable

Hosted file

`Figure.docx` available at https://authorea.com/users/740656/articles/713419-association-between-use-of-romosozumab-and-cardiovascular-events-analysis-of-the-japanese-adverse-event-report-database