Real-world effects, safety, and predictors of the effectiveness of romosozumab in primary and secondary osteoporosis: An observational study

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INTRODUCTION:

Romosozumab is an anti-sclerostin antibody that first became available in clinical practice in Japan in March 2019 for patients with osteoporosis at high risk of fracture. Romosozumab inhibits suppression of Wnt signaling and has the dual effect of promoting bone formation and decreasing bone resorption. Although the pivotal studies demonstrated the efficacy and safety of romosozumab, data on its use in the real-world setting are limited.

The aims of the study were two-fold: (1) to further elucidate the effects of 12 months of treatment with romosozumab by investigating its actual clinical effects, adverse events, and factors that independently predict its effectiveness, in particular the percent change in BMD from baseline and the kinetics of bone turnover markers during 12 months of treatment; and (2) to clarify the influence of pretreatment and whether osteoporosis is primary or secondary on the effects of 12 months of treatment with this agent.

METHODS:

1.1. Study design and participants

The study had a prospective observational design and enrolled 460 patients who were started on romosozumab for primary or secondary osteoporosis at our institution between March 2019 and June 2022. All patients received a subcutaneous injection of romosozumab 210 mg on entry into the study and monthly thereafter.

1.2.Study outcomes

The study was designed as a pre-post comparison of the study endpoints. The primary endpoints were the discontinuation rate, reasons for discontinuation, and adverse events. Information on adverse events was obtained from the interview at the point of discontinuation.

The secondary endpoints included patient characteristics, changes in BMD and serum bone metabolism markers, and the incidence of new fractures during 12 months of treatment with romosozumab. We also investigated whether previous treatment affected the results of the current treatment. According to the most recent antiosteoporosis agent administered before starting romosozumab, three pretreatment groups were defined: patients with no previous treatment for osteoporosis (treatment-naïve); those changed from teriparatide; and those changed from denosumab.

For more detailed analysis, the patients in each group were divided into those with primary osteoporosis and those with secondary osteoporosis. Changes in BMD were assessed by dual-energy X-ray absorptiometry using a PRODIGY Fuga-C densitometer (GE Healthcare, Tokyo, Japan). Areal BMD at the lumbar spine (L1–L4) and total hip was assessed at baseline and after 6 and 12 months of treatment with romosozumab. Previous fracture sites and sites at which orthopedic surgery had been performed were excluded. Data for patients who developed a bone fracture or underwent orthopedic surgery during the study were excluded from the BMD analysis. Serum biomarkers of bone metabolism were measured in the morning before administration of romosozumab at the start of treatment and 1, 3, 6, and 12 months later. Procollagen type 1 N-propeptide (P1NP) was used to assess bone formation and tartrate-resistant acid phosphatase 5b (TRACP-5b) for indirect assessment of bone resorption. Serum albumin-adjusted calcium, eGFR, and 25-hydroxyvitamin D (25OHD) were also measured. Finally, we examined factors that predicted or influenced the effects of treatment with romosozumab.

1.3. Statistical analysis

Patient background characteristics are expressed as the mean ± standard deviation. P1NP and TRACP-5b are shown as the median (interquartile range). Pre-post data were compared using the *t*-test if normally distributed. Unpaired samples were analyzed using the Mann–Whitney *U* test and statistical comparisons between the three groups were performed using the Kruskal–Wallis test with the Steel-Dwass test for post hoc comparisons. Statistical comparisons of rates between two groups were performed using Fisher's exact test. Independent predictors of the absolute increase in BMD at the lumbar spine after 12 months of treatment were sought using stepwise multiple regression analysis. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatics. P-values <0.05 were considered statistically significant.

RESULTS:

A total of 460 patients were initially enrolled. During the study period, 94 patients (20.4%) discontinued romosozumab because of adverse events (n=34, 7.4%), change to another hospital (n=32, 7.0%), self-withdrawal (n=19, 4.1%), financial constraints (n=7, 1.5%), and unrelated mortality (n=2, 0.43%).

The remaining 366 patients completed 12 months of treatment with romosozumab and were included in all subsequent analyses. New fractures occurred in 11 cases (3.0%). Nine patients (2.0%) experienced cardiovascular events, which

were fatal in 3 (0.65%). All CVs occurred from the secondary osteoporosis groups, and there were no differences in prevalence rates among the three pretreatment groups. All 9 cases had a history of comorbid disease (diabetes mellitus, n=4; chronic kidney disease, n=5). Two of the deaths and 3 of the nonfatal events occurred in patients on maintenance hemodialysis. Percent changes in BMD at the spine and total hip at 12 months from baseline were +7.7% and +1.8%, respectively. Romosozumab had better effects in patients with good renal function, low spine BMD, and high TRACP-5b at baseline and low TRACP-5b or high P1NP after 1 month of treatment. The percent change in spine BMD at 12 months was significantly lower in patients transitioning from denosumab than in those not previously treated with other anti-osteoporosis agents.
DISCUSSION AND CONCLUSION: Romosozumab is considered to be relatively safe in patients with primary osteoporosis compared to those with secondary osteoporosis. Romosozumab resulted in larger increases in spine BMD in patients with primary osteoporosis who were not previously treated with other anti-osteoporosis therapies and those with low spine BMD at the start of treatment.