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Re-evaluating Cardiovascular Risk in Osteoporotic Patients: A Case for Individualized Romosozumab Therapy

Osteoporozlu Hastalarda Kardiyovasküler Riskin Yeniden Değerlendirilmesi: Kişiselleştirilmiş Romosozumab Tedavisinin Önemi

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Dear Editor,

The cardiovascular safety profile of romosozumab is contentious issue, especially in light of findings from the ARCH trial suggesting a higher risk of the major adverse cardiovascular events (MACE) with romosozumab versus alendronate. Indeed, despite the impressive anti-fracture efficacy for romosozumab, its cardiovascular impact has led regulatory bodies to suggest cautious prescriptions or no recommendations at all. However, the cardiovascular risk may not be attributable to romosozumab per se but rather to baseline patient characteristics and study design, several real-world evidence and observational studies indicate (1).

Our patient is an 80-year-old lady with advanced osteoporosis who was previously treated for a year with ibandronate followed by a year of denosumab prior to being switched to romosozumab.

Notably, during denosumab treatment, the patient did not experience any adverse effects or new fractures. However, given the severity of her osteoporosis—including multiple vertebral compression fractures (T7, T9, T11, and L2) that required spinal stabilization surgery—her overall fracture risk remained substantially high. Therefore, a decision was made to escalate therapy by transitioning to romosozumab—an agent with both anabolic and antiresorptive effects—after prior use of antiresorptive agents including both bisphosphonates and denosumab. This switch reflected an individualized treatment approach tailored to the patient's persistently high fracture risk and therapeutic history.

She also had a history of hypertension and cardiac arrhythmia and had had cardiac ablation 1 year earlier. She was receiving apixaban for anticoagulation. Although she had a history of cardiovascular disease, cardiology clearance was obtained to initiate romosozumab. Her kidney function was normal (glomerular filtration rate: 65), as were her liver enzymes (alanine transaminase: 17, aspartate transaminase: 22), vitamin D (36 ng/mL) and calcium levels (9.64 mg/dL). During treatment with romosozumab, after 4 doses, no major cardiovascular events occurred on study.

After four doses of romosozumab (approximately six months of treatment), bone mineral density (BMD) improvements were observed. In the lumbar spine (L1-L4), the T-score improved from -5.15 to -4.16, and BMD increased from 0.445 g/cm² to 0.543 g/cm², reflecting a 22% relative gain. At the femoral neck, the T-score remained stable (-4.18 to -4.16), with a slight BMD increase from 0.376 g/cm² to 0.398 g/cm² (approximately 6% relative gain). These findings indicate a skeletal response, particularly in the spine, even after a relatively short course of romosozumab. No adverse events or new fractures were reported during this period.

This case highlights important points:

1. Romosozumab may still be an option in select high-risk cardiovascular patients if appropriate cardiology consultation and monitoring are performed.

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2. Real-world data on romosozumab use in high-cardiovascular-risk patients is needed, as controlled trials often exclude such individuals.

The discordant cardiovascular safety profile of romosozumab relates primarily to differences between clinical trials. The ARCH trial showed a statistically significant increase in MACE (hazard ratio: 1.87; 95% confidence intercal: 1.11-3.17; p=0.02) compared to alendronate given for 12 months, raising concerns regarding whether romosozumab may be pro-atherosclerotic (1). The FRAME trial, which compared romosozumab with placebo, found no difference in cardiovascular events (MACE 0.8% in both groups), suggesting that the potential cardioprotective effect of alendronate may have confounded the ARCH trial results (1). Moreover, the BRIDGE trial, which involved men with osteoporosis, showed a higher rate for cardiovascular events in users of romosozumab (4.9%) compared to placebo (2.5%), but did not achieve statistical significance (2).

Recent real-world data from a large propensity-score-matched cohort study (TriNetX, covering 136 million patients) provides additional insights. This study compared romosozumab with parathyroid hormone (PTH) analogues (teriparatide/abaloparatide) and found that romosozumab was associated with fewer major cardiovascular events than PTH analogues, challenging the assumption that romosozumab inherently increases cardiovascular risk (3). Also, an unusual frequency of cardiovascular events was noted as reported in Food and Drug Administration (FDA) adverse event reporting system pharmacovigilance studies in Japan, possibly attributable to higher baseline cardiovascular risk in patients in Japan, rather than being directly attributable to romosozumab (3).

Mechanistic hypotheses exist for sclerostin inhibition influencing vascular calcification and progression of atherosclerotic cardiovascular disease given that it is expressed in vascular smooth muscle cells. Yet definitive cardiovascular dysfunction with romosozumab has not been demonstrated in preclinical studies, and Mendelian randomization studies have been conflicting, showing that lower sclerostin associates with an increased risk of atherosclerosis but failing to show definitive causation (4).

Given these findings, a one-size-fits-all approach to cardiovascular risk and romosozumab may not be appropriate. Regulatory agencies have taken a cautious stance—the FDA recommends avoiding romosozumab in patients with a history of MI or stroke within the past year, while the EMA contraindicates its use in all patients with prior cardiovascular events. But increasing real-world evidence suggests that careful patient selection and multidisciplinary oversight may allow high-fracture-risk patients with stable cardiovascular conditions to take romosozumab with no undue risk (1).

In summary, this case highlights the importance of providing thoughtful consideration of risk-to-benefit ratio in selecting osteoporosis therapy in patients with concomitant cardiovascular disease. While regulatory guidelines err on the side of caution, clinicians should integrate real-world data, patient-specific cardiovascular profiles, and multidisciplinary decision-making when considering romosozumab therapy. Large-scale observational studies and prospective trials will be needed to further optimize patient selection and treatment safety.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.F.B., E.C., Concept: F.B., Design: R.Ç., F.B., Data Collection or Processing: F.B., Analysis or Interpretation: M.H.T., E.C., Literature Search: R.Ç., M.H.T., Writing: F.B.

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