EDITORIALS

Romosozumab — Promising or Practice Changing?

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Over the past decade, the osteoporosis landscape has changed. Even though more treatment options are available, fewer measurements of bone mass are being performed and fewer prescriptions for antiosteoporosis agents are being written — the last probably related to concerns about known side effects of bisphosphonates, such as atypical femoral fractures and osteonecrosis of the jaw. Even among patients with osteoporosis who have had a fracture and are then prescribed bisphosphonates, 70% are nonadherent within a year.[1] Denosumab, another antiresorptive agent with proven efficacy, is rarely associated with atypical fractures and requires that patients continue to receive therapy indefinitely. Teriparatide, a recombinant human parathyroid hormone analogue, prevents fractures, but its protective effects wane beyond 2 years, its price has quadrupled over the past decade and a half, and insurers remain hesitant about reimbursement. All these issues have resulted in a gap in osteoporosis care.

Three new drugs have shown promising results in phase 3 trials, raising our expectations of closing that gap. However, of these agents, only abaloparatide, a parathyroid hormone–related peptide analogue, has been approved by the Food and Drug Administration (FDA). Abaloparatide, with a mechanism analogous to that of teriparatide, reduces both spine and hip fractures and has a nearly identical safety profile.[2] Odanacatib, a cathepsin K antagonist with some bone-forming properties, was recently withdrawn from FDA consideration, owing to an elevated incidence of stroke, despite strong beneficial effects on fracture risk. The third agent, romosozumab, a monoclonal antisclerostin antibody, was compared with alendronate in the phase 3 Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk (ARCH), which is now described by Saag et al. in the *Journal*.[3]

Romosozumab was developed on the basis of the seminal finding in 2001 that sclerosteosis, a rare genetic disorder with high bone mass, was associated with a loss-of-function mutation in *SOST*, the gene that encodes sclerostin.[4] Sclerostin is produced by osteocytes, inhibits bone formation, and enhances bone resorption, primarily by binding to low-density lipoprotein receptor–related protein (LRP) 4, 5, and 6, the receptors for Wnt ligands. In an earlier phase 3, randomized, placebo-controlled trial (Fracture Study in Postmenopausal Women with Osteoporosis [FRAME]), 1 year of romosozumab administered monthly increased bone mineral density at the lumbar spine by 13%, and the risk of new vertebral fracture was 73% lower with romosozumab than with placebo.[5] The marked increase in bone mineral density was attributed to increased bone formation and decreased bone resorption.

In ARCH, Saag and colleagues randomly assigned more than 4000 postmenopausal women at very high risk for fractures to receive monthly subcutaneous romosozumab or weekly oral alendronate during the first year of the trial, and all the women received open-label alendronate during the second year. Over a period of 24 months, the risk of new vertebral fracture was 48% lower in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group. At the time of the primary analysis, the risks of other fracture end points were significantly lower in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group, with a lower risk of clinical fracture (by 27%), nonvertebral fracture (by 19%), and hip fracture (by 38%). Hence, romosozumab followed by alendronate appeared to be more efficacious than alendronate alone for the treatment of established osteoporosis.

However, in ARCH, there were more adjudicated serious cardiovascular adverse events with

romosozumab than with alendronate, whereas in FRAME, the incidence of such events was balanced in the romosozumab and placebo groups. One possible mechanism underlying such events could be a role for sclerostin in vascular smooth muscle, a concept that comes from studies showing that *SOST* is expressed in other tissues, including aortic vascular smooth muscle. Thus, inhibition of sclerostin by romosozumab could potentially alter vascular remodeling that is normally induced by the Wnt signaling pathway.[6] In addition, sclerostin is up-regulated at sites of vascular calcification, although its pathogenic role there is not defined. Another possibility, albeit remote, is that the comparison drug, alendronate, is cardioprotective, and therefore the rate of cardiovascular events in the romosozumab group appears relatively higher than expected. However, several meta-analyses of randomized, controlled trials of alendronate have not shown a decrease in cardiovascular events. Finally, the number of adverse events was small, leading to the possibility of a type I error, since the trial was not powered to test noninferiority versus alendronate for safety.

What can we learn from this trial, which is unique as a fracture efficacy trial comparing a new bone-active drug with a long-established therapy — a true comparative-effectiveness trial? Romosozumab is very effective in preventing fractures among high-risk postmenopausal women, particularly when taken for 1 year followed by alendronate. Romosozumab has strong antiresorptive properties, although it is unclear whether the sequence of romosozumab followed by alendronate increases the risk of atypical femoral fractures. Finally, the cardiovascular signal for romosozumab is particularly troubling. Although it may be surprising that a bone-specific drug has off-target cardiovascular effects, this finding is very consistent with our recent understanding of the skeleton as an endocrine tissue that modulates whole-body homeostasis by secreting peptides such as sclerostin, fibroblast growth factor 23 (FGF-23), and osteocalcin. Moreover, other bone-targeted therapies, including estrogen and odanacatib, have adverse cardiovascular effects.

In sum, ARCH revealed that romosozumab has great potential as a short-term anabolic treatment for osteoporosis. However, until the cardiovascular and endocrine effects of this antibody are clarified, romosozumab will remain more a part of our expectations than our armamentarium.

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Handle Survivors with Care

Armand Sprecher, M.D., M.P.H.

In 1967, a woman became ill after exposure to a newly discovered pathogen that we now call Marburg virus, a member of the family Filoviridae (filoviruses), to which Ebola virus also belongs.[1] Testing of the semen of her husband, who had recovered from the disease 6 weeks previously, determined that her exposure was through sexual intercourse. This was the first confirmed case of sexual transmission of filovirus disease from a convalescent man. It was also the last . . . until the West African outbreak.

In March 2015, Ebola virus disease (EVD) developed in a Liberian woman after the country had been free from EVD for 30 days.[2] This woman had no identifiable risk factors for EVD other than sexual contact with a male survivor of the disease. This survivor's semen tested positive for Ebola virus RNA, which suggested sexual trans-