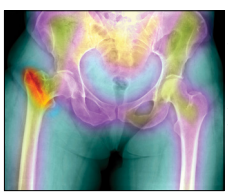
Bone-forming agents in non-responders to bisphosphonates



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Osteoporosis is a chronic disease requiring long-term treatment. Oral bisphosphonates, which act by inhibiting bone resorption, are most commonly prescribed but inadequate response, development of intolerance, or fear of long-term side-effects sometimes necessitate change to an alternative therapy.[1] One option is to switch to teriparatide, a bone-forming agent, but enthusiasm for this strategy is tempered by the blunting of the bone mineral density (BMD) response to teriparatide seen in patients previously treated with antiresorptives.[2–4]

Romosozumab (AMG 785) is a monoclonal antibody that binds to and inhibits sclerostin, a negative regulator of bone formation. In addition to stimulating bone formation, it also inhibits bone resorption. Previous studies have shown that in postmenopausal women with low bone mass, treatment with romosozumab 210 mg subcutaneously for 12 months resulted in significantly greater increases in hip and spine BMD than did treatment with teriparatide, and in postmenopausal women with osteoporosis, treatment for 12 months with this dose of romosozumab significantly reduced vertebral and clinical fractures compared with placebo.[5,6] Romosozumab is awaiting regulatory approval in the USA, Canada, and Japan, although because of an imbalance in serious adverse cardiovascular events in the ARCH study a decision is not expected until 2018.[7]

Against this background, in a randomised open-label study in 436 postmenopausal women who were previously treated with oral bisphosphonates for a mean duration of 6·2 years, Bente Langdahl and colleagues[8] compared the effect of transitioning to 12 months' treatment with teriparatide or romosozumab. Despite earlier bisphosphonate therapy, these women all had osteoporosis (BMD T score ≤–2·5) and a history of fracture after the age of 50 years. For the primary endpoint, percentage change from baseline in areal BMD by dual-energy x-ray absorptiometry at the total hip up to month 12, romosozumab was significantly superior to teriparatide (change +2·6% in the romosozumab group *vs* –0·6% in the teriparatide group; p<0·0001). Cortical hip volumetric BMD increased at 6 and 12 months in women treated with romosozumab, but decreased in those treated with teriparatide. Hip strength, estimated by finite element analysis, was significantly increased at both timepoints in the romosozumab group, whereas in women receiving teriparatide a significant decline was seen at 6 months and the mean value remained below baseline at 12 months. Adverse events, including fractures (reported as serious adverse events), were generally balanced between groups.

Comparison of the effects on hip BMD of transitioning to romosozumab or teriparatide is of particular interest in view of the decline in hip BMD previously reported in several studies of sequential exposure to bisphosphonates and teriparatide.[2–4] The study by Langdahl and colleagues supports and extends this finding, providing additional information about changes in hip cortical and trabecular bone. Transition to teriparatide was accompanied by a decrease in cortical volumetric BMD and an increase in trabecular volumetric BMD; although there was little overall change in integral (cortical plus trabecular) volumetric BMD, bone strength estimated by finite element analysis decreased. By contrast, transition to romosozumab was associated with an increase in hip cortical and trabecular volumetric BMD, and in hip strength. These opposing effects of the two drugs on hip cortical bone might reflect differing mechanisms of action. The anabolic effects of teriparatide depend to a large extent on its pro-remodelling activity, and the decline in hip cortical BMD might be caused by increased cortical porosity and reduced mineralisation of newly formed bone.[9,10] By contrast, changes associated with romosozumab might be mediated more by modelling-based bone formation, accompanied by inhibition of bone resorption and hence suppression of bone remodelling.[11] However, increases in bone density and strength resulting from prolonged therapy with teriparatide, which is approved for up to 2 years of treatment, cannot be excluded on the basis of this 12-month study.

In clinical practice, it is not uncommon to encounter patients who despite adequate adherence to medication apparently do not respond to oral bisphosphonates, with persistently low BMD or incident fracture during treatment. Some of these patients might respond to intravenous bisphosphonate therapy, but in others switching to a drug that stimulates bone formation is a reasonable approach. Although the effects on fracture risk have not been established, the results of the study by Langdahl and colleagues suggest that the greatest benefits for hip BMD and estimated strength are obtained

with a drug such as romosozumab that stimulates bone formation and inhibits bone resorption. Use of sequential therapy in osteoporosis is the focus of much attention,[12] and this study shows the potential for the use of drugs with different mechanisms of action as a strategy to improve outcomes in the management of osteoporosis. Since the duration of therapy with bone-forming agents is limited and bone loss follows treatment withdrawal, the subsequent use of interventions to maintain treatment benefits is an important area for future research.

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I have received advisory and speaking fees from Gilead related to tenofovir alafenamide, a new antiretroviral agent for treatment of HIV infection, and speaking fees from Amgen for a talk on the treatment gap in osteoporosis.

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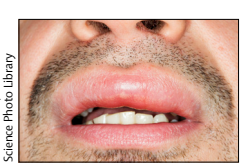
Recombinant human C1 esterase inhibitor for hereditary angio-oedema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Patients with the autosomal inheritable disease hereditary angio-oedema have recurrent swelling of subcutaneous and cutaneous tissues. The frequency of attacks varies enormously between individuals and can range from a few swellings per year to multiple attacks per week. In most cases, acute treatment is sufficient, but prophylactic treatment can reduce the burden of illness for severely impaired patients.[1] Available treatments for hereditary angio-oedema prophylaxis comprise either plasma-derived C1 esterase inhibitor concentrates or attenuated androgens, such as danazol.[2] Treatment with attenuated androgens is associated with serious dose-related adverse effects, including voice changes, hirsutism, and cardiovascular and hepatic side-effects.[3]

In *The Lancet,* Marc Riedl and colleagues' phase 2, multicentre, randomised, double-blind, placebo-controlled, three-arm crossover trial[4] examines the efficacy and safety of recombinant human C1 esterase inhibitor—a new prophylactic treatment option for hereditary angio-oedema. Patients with hereditary angio-oedema (aged ≥13 years) were treated in different periods of treatment sequences with recombinant human C1 esterase inhibitor 50 IU/kg once weekly plus placebo once weekly versus recombinant human C1 esterase inhibitor 50 IU/kg twice weekly versus placebo twice weekly. Each sequence was separated by a 1 week washout period. The primary endpoint was the number of attacks of hereditary angio-oedema per 4 week treatment period.

The mean number of attacks was significantly reduced with recombinant human C1 esterase inhibitor, when given both twice weekly (mean difference −4·4 attacks; p<0·0001) and once weekly (−2·8 attacks; p=0·0004) versus placebo (7·2 attacks [SD 3·6]). Moreover, the twice-weekly regimen was more effective than