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MEETING REPORT

Recent progress in osteoporosis treatment (IBMS/JSBMR joint meeting 2013)

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Introduction

Osteoporosis treatment is one of the main targets to be investigated in the field of bone and mineral research. Accumulating clinical evidence indicates that anti-fracture efficacy of bisphosphonates, selective estrogen receptor modulators (SERMs), teriparatide and some other agents has been established, and they are now widely prescribed. However, there still remain clinical needs for osteoporosis treatment, that is, efficacy and safety of drugs should be improved. Actually, we need more powerful and safer tools to prevent fractures in elderly people. In the 2nd Joint Meeting of IBMS and JSBMR, many studies of several drugs not only already available in daily practice, such as denosumab, eldecalcitol and teriparatide, but also upcoming and under development have been presented. This is a report of recent progresses in osteoporosis treatment presented in the meeting.

Denosumab

The receptor activator of nuclear factor-kappaB ligand (RANKL) is a key molecule of bone resorption. Denosumab is a fully humanized monoclonal antibody against RANKL and is licensed for the treatment of osteoporosis. The FREEDOM Trial that included 7868 osteoporotic women is a pivotal clinical study to demonstrate that administration of denosumab for 36 months significantly decreased vertebral by 68%, non-vertebral by 20% and hip fractures by 40%. It has been extended to 10 years, and anti-fracture effects of denosumab have been reported to be still significant at 5 years.[1] Denosumab has also been shown to be effective in male osteoporosis, including men treated with androgen deprivation drugs for prostate cancer and for women who take aromatase inhibitors for breast cancer. As denosumab inhibits bone resorption more powerfully than bisphosphonates, such as alendronate, health-care providers should be aware of the risks of atypical fracture and osteonecrosis of the jaw when patients are treated with denosumab. Furthermore, they are in charge to watch patients carefully, because it may decrease serum calcium level significantly within a week or so.

Eldecalcitol

Elderly osteoporotic patients suffer from a large negative balance in calcium metabolism by a decrease in the intestinal calcium absorption, in addition to the negative balance in bone remodeling. Thus, vitamin D actions are critically involved in bone health. However, the effect of native vitamin D on fracture prevention in osteoporotic patients is small, if any. Vitamin D is activated to 1,25-dihydroxyvitamin D to exert its actions via the binding to its specific nuclear receptor, VDR. Eldecalcitol, an analog of 1,25-dihydroxyvitamin D that strongly activates VDR, has been developed and shown to be effective to prevent vertebral fractures in Japanese osteoporotic patients.[2] Treatment with eldecalcitol increases bone mineral density (BMD) and decreases vertebral fractures more efficiently than alfacalcidol. Eldecalcitol suppresses osteoclastogenesis *in vitro* in mice and decreases bone resorption markers in human in comparison with alfacalcidol when the former similarly stimulates calcium absorption to the latter. It is yet to be elucidated the mechanism whereby eldecalcitol inhibits osteoclastic bone resorption.

Teriparatide

Teriparatide is the only anabolic agent in practice that stimulates bone formation to increase BMD and prevent fractures. Recently, bisphosphonate-related atypical femoral fracture has been increasing concerns on osteoporosis treatment. A retrospective and observational study has been reported to suggest that the use of teriparatide could be an option during conservative treatment for incomplete atypical femoral fracture to prevent requirement of surgical fixation.[3] As bisphosphonate-related atypical fracture is uncommon but a serious issue that should be resolved in daily practice, this report promotes prospective clinical studies to verify the efficacy of teriparatide for the specific health concern.

Odanacatib

Conventional anti-resorptive drugs, such as bisphosphonates, for osteoporosis suppress osteoclast activity in general resulting

in the decrease in bone formation by osteoblasts. Cathepsin inhibitors presenting rigorous specificity to cathepsin K might reduce bone resorption along with relative preservation of bone formation. Odanacatib is a selective cathepsin K inhibitor and now is under development for the indication in osteoporosis. A phase 2 clinical trial has been extended, and the 5-year data demonstrate significant and sustained decreases in bone resorption markers, although TRACP-5b levels, a marker for osteoclast viability, were not suppressed. Bone formation markers decreased only temporarily and then increased toward baseline levels. Unlike bisphosphonates, BMD increased progressively at the lumbar spine and femoral neck at least for 5 years. A placebo-controlled phase 3 trial with a primary end point of fracture prevention was conducted with more than 16 000 subjects. An interim analysis of the study has shown significant effects that prevent fractures.[4] Furthermore, treatment with odanacatib for 2 years has been demonstrated to provide incremental BMD gains in osteoporotic women following alendronate treatment.[5] In another clinical study, odanacatib has been shown to increase estimated strength, cortical and trabecular BMD and cortical thickness of the distal radius and tibia compared with placebo.[6]

Anti-sclerostin Antibodies

Administration of antibodies that neutralize sclerostin, an inhibitor of Wnt/β-catenin signaling in osteoblasts, has been shown to increase bone mass. Subcutaneous injections of the human sclerostin antibody blosozumab, developed by Eli-Lily and Co., has been reported to increase BMD in Japanese and non-Japanese postmenopausal women with low BMD at 52 weeks.[7] The increment of BMD was significant and 17.75% at lumbar spine and 6.70% at total hip.

Another anti-sclerostin antibody romosozumab, developed by Amgen Inc., has also been investigated in human. Administration of romosozumab to postmenopausal women has been shown to increase bone formation markers and decrease bone resorption markers, maximizing BMD increases.[8]

As human diseases resulting from genetic inactivation of *SOST* demonstrate high bone mass but not other serious health problems, neutralizing antibodies against sclerostin, a product of *SOST* gene, could be a powerful and promising therapeutic tool for osteoporosis treatment.

Conflict of Interest

YT has received speakers fee from Chugai Pharmaceutical Co., Daiichi-Sankyo Co., MSD and Eli-Lily Japan Co.

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