Denosumab: not only postmenopausal osteoporosis

M. Rossini, Rheumatology Unit University of Verona, Verona

The regulation of bone mass in mammals is governed by a complex interplay between bone-forming cells termed osteoblasts and bone-resorbing cells termed osteoclasts, and is guided physiologically by a diverse set of hormones, cytokines and growth factors. Osteoclasts and osteoblasts define skeletal mass, structure and strength through their respective actions in resorbing and forming bone. This remodeling process is orchestrated by the actions of hormones and growth factors, which regulate a cytokine system comprising the receptor activator of nuclear factor κB ligand (RANKL), its receptor RANK and the soluble decoy receptor osteoprotegerin (OPG). Bone resorption depends on RANKL, which determines osteoclast formation, activity and survival. Importantly, cells of the osteoblastic lineage mainly provide RANKL and therefore, are central in the regulation of osteoclast functions. Catabolic effects of RANKL are inhibited by OPG, a TNF receptor family member that binds RANKL, thereby preventing the activation of its receptor RANK, which is expressed by osteoclast precursors. Because this cytokine network is pivotal for the regulation of bone mass in health and diseases, including osteoporosis, rheumatoid arthritis and malignant bone conditions, it has been successfully used for the generation of a targeted therapy to block osteoclast actions. The clinical approval of denosumab, a fully monoclonal antibody against RANKL, provides a novel option to treat bone diseases with a potent, targeted and reversible inhibitor of bone resorption. Using advanced gene-engineering techniques, Amgen Inc. (USA) has developed the drug, and it is now utilized for treatment of osteoporosis, cancerous bone lesions associated with multiple myeloma and bone metastasis. On the other hand, denosumab has also shown inhibitory effects on bone resorption seen in patients with other diseases involving bone, as rheumatoid arthritis and systemic mastocytosis, thus its range of use for medical treatment is expected to widen. Because of its long half-life and pharmacokinetics, subcutaneous denosumab administrations every 6 months are sufficient to obtain potent and diffuse inhibitory effects on bone resorption, suggesting that this agent is more efficacious than bisphosphonates, which are presently used as anti-bone resorptive drugs. With its novel mechanism of action, denosumab offers a significant advance not only in the treatment of postmenopausal osteoporosis but also in bone loss associated with hormone ablation therapy in women with breast cancer and men with prostate cancer, and for the prevention of skeletal-related events in various diseases.