

Anti-sclerostin antibodies and the future treatment of osteoporosis.

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Osteoporosis is a bone disorder characterized by the reduction of bone mass and/or volume in a normally mineralized bone. This ultimately results in reduction in the mechanical strength of bone making it more vulnerable to minimal trauma fracture [1]. Osteoporosis is highly prevalent in elderly especially postmenopausal women and it can increase both morbidity and mortality. It is estimated that over 200 million adults have osteoporosis worldwide. Furthermore, the prevalence of osteoporotic fractures is increasing by 1% to 3% each year worldwide [2]. Therefore effective and novel treatments are required to overcome this global health problem.

Sclerostin is a glycoprotein produced almost exclusively from mature osteocytes and acts by inhibition of the Wnt signaling pathway which plays a critical role in osteoblast development and function and hence, sclerostin is a powerful inhibitor of bone formation [3]. The discovery of this important molecule was the result of extensive research of the genetics of two familial disorders, Sclerosteosis and Van Buchem disease, which are characterized by increased bone mineral density, tall stature and entrapment of cranial nerves due to overgrowth of a highly dense bone [4]. Van Buchem disease was initially described in 1955, and it appears more frequently in persons of Dutch ancestry. The level of sclerostin is low or undetectable in those people due to a defect in the genes on chromosome region 17q12-q21 [4]. As a result a process of unopposed and excessive bone growth and increased bone strength is seen. This notion led the scientists to induce sclerostin deficiency in mice which reproduced the bone sclerosing human diseases. On the other hand, sclerostin excess leads to bone loss and reduced bone strength.

Modulating sclerostin activity through the use of neutralizing antibodies is being investigated as a mean of treating osteoporosis. Anti-sclerostin antibody treatment has been shown to increase bone formation, mass, and strength while suppressing bone resorption in rat and monkey models displaying clear anabolic effects with significant increases in bone formation on trabecular, periosteal, endocortical and intracortical surfaces [5]. Furthermore, anti-sclerostin antibodies have been reported to enhance fracture-healing and implant fixation in other studies [3]. The treatment was associated with an approximately five to sevenfold increase in the bone-formation rate and a >50% depression in the eroded surface. Trabecular bone thickness was increased significantly in the treated mice [3].

In humans, Clinical phase II and III trials are currently underway thereby translating human genetics to drug development [6-9]. Two agents are being tested; romosozumab (Amgen) and blosozumab (Eli Lilly), and the results are very promising as expected from preclinical models studies [7-10]. The agents are given either subcutaneously or intravenously with a frequency of dosing between 2 weeks and 3 months. Both of the drugs showed superiority to other pre-existing therapies like

antiresorptive (bisphosphonates and denosumab) and anabolic (teriparatide) with a side effects profile comparable to placebo [7-10]. The results of phase II trial of subcutaneously injected romosozumab in 419 postmenopausal women with a period of follow up of 12 months has been recently published [7]. The dose of 210 mg of romosozumab monthly significantly increased bone mass at all skeletal sites (11.3% at the spine, 4.1% at the hip and 3.7% at the femoral neck [7]).

Accordingly, it has been suggested that Anti-sclerostin antibodies will achieve market approval by 2017 and will become the first drug of choice for treating osteoporosis by 2021.

The discovery of sclerostin and its role in bone formation is of pivotal clinical benefits not only from the therapeutic point of view but also the diagnostic one. Serum sclerostin levels have been positively associated with increased fracture risk and hence can be used as a marker for fracture risk assessment. Currently there are three commercial sclerostin assays available [4].

The future of anti-sclerostin antibody treatment and plasma sclerostin blood test is promising. All the scientist and clinicians with an interest in the field of osteoporosis are awaiting the ultimate results of ongoing clinical trials.

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