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Review Article

A view at monoclonal antibodies in therapy of osteoporosis

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ABSTRACT

Introduction: Osteoporosis is a bone disease, which leads to increased fracture risk and weakens bone strength. Drugs used in current therapies of this disease are far from perfect thus the search for new effective compounds is an ongoing process, and some researchers put great hopes in monoclonal antibodies in this field.
Aim: The purpose of this paper is to discuss monoclonal antibodies as potentially beneficial therapy of osteoporosis.
Material and methods: It was based upon the available literature and publications.
Results and discussion: Sclerostin is a glycoprotein that belongs to Wnt inhibitors. Wnt/β-catenin signaling pathway is essential for normal physiological cell functions such as differentiation or proliferation. Inhibition of sclerostin activity can result in increased bone mineral density, and can be achieved by using antibodies against this factor, i.e. romosozumab and blosozumab. Another compound that has an influence on Wnt/β-catenin signaling pathway is Dickkopf-1. Monoclonal antibodies against this factor have been tested in bone diseases and found to contribute to increased bone mineral density. Other anti-resorptive agent indicated for the treatment of osteoporosis is a receptor activator of nuclear factor-κB ligand (RANKL) inhibitor. Denosumab is a human antibody to RANKL, and it decreases osteoclastogenesis and osteoclast activity, leading to reduced bone resorption. It is currently used in treatment of postmenopausal osteoporosis.
Conclusions: The essential goal for the management of osteoporosis is to increase bone mass and reduce fracture risk by slowing or stopping bone loss. Monoclonal antibodies that have been recently developed are becoming an important option in the pharmacotherapy of osteoporosis.

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1. Introduction

Monoclonal antibodies are a group of biological agents that are hugely important in targeted therapies for many disorders. They specifically bind to exact targets, allowing improvement of clinical efficacy and safety. These developmental drugs, which in fact are immunoglobulins that modify immunological reaction, have become useful not only in cancer treatment, but also in treatment for other diseases including multiple sclerosis, psoriasis, age-related macular degeneration, rheumatoid arthritis and osteoporosis.[1]

Osteoporosis is a bone disease that affects both women and men. Its clear characteristics such as low bone mass and disturbed bone microarchitecture are caused by a lack of balance between the actions of osteoblasts and osteoclasts. All of these disturbances lead to increased fracture risk, and weaken bone strength.[2]

Nowadays, drugs with anti-resorptive or stimulating bone formation properties are used to prevent possible fractures and avoid any significant reduction in quality of life of osteoporotic patients. Despite all the benefits, drugs used in current therapies are far from perfect thus the search for new effective compounds is an ongoing process, and some researchers put great hopes in monoclonal antibodies in this field.[1]

2. Aim

This article discusses monoclonal antibodies that are currently being used or tested in the therapy of osteoporosis and other bone diseases, as promising therapeutic methods.

3. Material and methods

This article was based on the available literature and publications.

4. Results and discussion

4.1. *Anti-sclerostin antibodies*

The progress in discovery of mechanisms that are at the heart of the imbalance between bone formation and bone resorption contributes to development of new drugs, e.g. monoclonal antibodies against sclerostin.

Sclerostin is a glycoprotein codified by the human SOST gene and is considered to be a member of the DAN family of bone morphogenetic protein antagonists. In the structure of this compound the C-terminal cysteine knot-like domain can be distinguished. Sclerostin is not only a monomeric protein, what Hernandez et al. showed in their work, but also occurs in other forms like dimers. Moreover, they described the sclerostin molecular weight to be detected more often as 47 kDa, 54 kDa or 70 kDa rather than the 27 kDa mentioned in former works.[3–5]

For a long time sclerostin was considered to be produced exclusively by osteocytes; however the SOST mRNA has been discovered in several parts of the organism such as kidneys, heart, lungs, liver, aorta, and chondrocytes. Nonetheless, osteocytes are still the main producers of glycoprotein, which in its 54 kDa dimeric form can be secreted from the bone and spread into various organs.[3–8]

Serum sclerostin levels depend on many factors, and increase with age or augmentation of fat mass; it can also be higher in men. Increased levels can also be observed in conditions such as type 2 diabetes, atherosclerosis or aortic calcifications.[6–10]

In contrast to those conditions, some disorders are associated with reduced serum sclerostin levels. Cases in point are sclerosteosis and van Buchem's disease – both are caused by mutations of the SOST gene and the decreased level of sclerostin that follows. In sclerosteosis two clinical phenotypes can be observed. As opposed to heterozygotes that are defined by reduced level of sclerostin, homozygotes' serum sclerostin level is undetectable. Furthermore, severe symptoms occur in homozygotes, including bone overgrowth, facial nerve paralysis or syndactyly. In heterozygotes none of these appear. They are phenotypically normal, and only aberrations that can be observable are higher than normal bone mass and rarely fracture. Contrary to sclerosteosis, van Buchem's disease is characterized by low levels of sclerostin in all patients, which results in increased bone mass and other similar but less severe symptoms. All skeletal disturbances in mentioned disorders are associated with sclerostin, and can be explained by physiological functions of this compound.[5,11]

Nowadays, it has become well-known that sclerostin belongs to Wnt inhibitors. Wnt/β-catenin signaling pathway is essential for normal physiological cell functions such as differentiation or proliferation. Sclerostin is a protein, which is able to bind to Wnt co-receptors low-density lipoprotein receptor-related protein (LRP) 5/6, causing receptor internalization through inhibition of β-catenin translocation into nucleus, and augmentation of β-catenin degradation. Regarding bones, Wnt pathway participates in balance maintenance between bone formation and resorption. The pathway stimulates osteoprotegerin (OPG), which results in counteracting excess bone resorption due to binding receptor activator of nuclear factor-κB ligand (RANKL). Besides LRP5 and LRP6, sclerostin can also bind to LRP4. Data from previous studies concerning LRP4 protein mutations showed occurrence of aberrations of skeletal phenotypes in the form of increased bone mass.[5,11–13]

Genetic modifications of sclerostin activity were observed both during researches, and in naturally occurred diseases such as sclerosteosis and van Buchem's disease. It was precisely its inhibition, resulting in increased bone mineral density (BMD) that opened up the possibility of therapeutic use of the observed effects. Monoclonal antibodies against sclerostin, through specific binding to this protein, can block its action and contribute to increased bone formation. Anti-sclerostin antibodies prevent binding of sclerostin to LRP6, as well as receptor internalization and degradation of β-catenin, all of which result in osteoanabolic effects. Amongst sclerostin antibodies there are blosozumab and romosozumab, which are the first humanized monoclonal antibodies against sclerostin.[5,9,13,14]

Phase I clinical trial in blosozumab in postmenopausal women was completed in 2014. Data indicated safety of a