Study Progress in the Application of Bone Targeting Drugs for the Treatment of Osteoporosis

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Abstract: Belongs to the metabolic disease with the highest incidence rate. The middle-aged and elderly people are the main disease group. Osteoporosis may lead to an increased risk of fracture. Currently, the drugs for clinical treatment of OP mainly on drugs of inhibiting the bone resorption and promoting bone synthesis. With the gradual deepening of the research on the etiology and pathogenesis of OP, the bone targeting drugs such as cytokines, hormones and peptides have been widely used in clinical practice. All of them have certain curative effects, but there are limitations in the use of various drugs. It is important to find a bone targeting drug with strong bone-affinity and stable structure to improve the symptoms of bone loss in patients. Based on the above background, this paper summarizes the application of bone targeting drugs to OP, summarizes the mechanism and efficacy of various drugs, and concludes and prospects future application trends, hoping to provide more options for clinical drug use.

OP is a pathological result caused by the imbalance of bone resorption and osteoblast formation mechanism of osteoclastic [1]. Bone resorption inhibitors and bone synthesis promoters are commonly used anti-OP drugs. The former can inhibit osteoclast activity, thereby reducing bone resorption, specific drug includes calcitonin, estrogen, bisphosphonate, selective estrogen receptor modulators, etc.; the latter can promote new bone formation as the main mechanism, specific drugs include the PTH and similar drugs, etc. With the progress of molecular medicine study at the molecular, especially the study of NF-κB signaling pathway, it provides a new way for the development of anti-OP drugs. The bone targeting drugs such as cytokines, hormones and peptides are gradually applied to anti-OP treatment. The following is a summary of reviewing the mechanisms and effects of the various drugs from the conceptual analysis perspective.

1. Conceptual Analysis of Bone Targeting Drugs

The bone is composed of a variety of cells and intercellular bone matrix, which is a very special connective tissue in the human body. The inorganic salt is high in the bone matrix, and the weight of the inorganic salt in the adult backbone accounts for about 70%, and the hydroxyapatite is its main ingredients. In addition, the content of calcium in the bone accounts for the vast majority of the total amount of calcium in the human body, up to 99%, and the existence form is substantially different from that of hydroxyapatite. According to the above features, a molecule that can specifically bind to hydroxyapatite is called a bone targeting drug carrier, and the carrier is to selectively act on bone tissue.

The concept of "bone targeting" was first clarified in 1986. Foreign scholars synthesized the first bone targeting effect by inhibiting carbonic anhydrase inhibition of acetylpyrazole with the hydroxyl group of tetracycline 12a by adipic acid chloride [2], and provides theoretical and experimental evidence for the study of the molecular drug WP-1, which has a slight effect on non-bone tissue as well as bone targeting drugs. Since then, tetracyclines, bisphosphonates, polymalonic

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acids, polypropylene diesters, etc. have been discovered in the study process based on bone targeting drugs. These carriers provide a basis for the clinical application of bone targeting drugs.

2. Mechanism and Effect of Various Bone Targeting Drugs in the Treatment of OP

2.1 Bone Resorption Inhibitor.

2.1.1 NF-κB receptor activating ligand/receptor signal transduction pathway inhibitor

2.1.1.1 Osteoprotegerin

The NF-κB receptor activating ligand belongs to the type I transmembrane protein and belongs to a superfamily with TNF, mainly expressed by osteoblasts and bone matrix cells, and receptors on mature osteoclasts and osteoclast precursor cells. Binding to mature osteoclasts and receptors on osteoclast precursor cells induces osteoclast formation and activation. When the NF-κB receptor activation ligand and receptor bind and are activated, the resulting signaling pathway will act along the binding of both and TNF receptor-associated family to activate NF-κB, JNK, c-src and many other nuclear factors, and through the serine-threonine kinase pathway to regulate osteoclast differentiation, therefore, inhibition of NF-κB receptor activation ligand receptor complex inhibits osteoclast overexpression. Osteoprotegerin is a member of the TNF receptor family lacking a transmembrane domain. It is a secreted glycoprotein containing 380 amino acids and soluble pseudo-receptors that can inhibit the formation, activation and survival of osteoclasts through competitive mechanisms with mature osteoclasts and receptors on osteoclast precursor cells, and reverse the effect on OP.

At present, the osteoprotegerin for clinical injection belongs to the fusion protein after gene recombination, and the ability to bind the NF-κB receptor to activate the ligand is similar to that of the natural osteoprotegerin. The experiments of Chuncai Cui [3] et al. indicate that the bone resorption was observed to decrease significantly within 12 hours after subcutaneously injected osteoprotegerin, and the bone resorption was down the least within 5 days. The mean decrease value of N-terminal peptide was within 14~15% within 6w, and the greater the dose, the stronger the effect of reducing bone resorption. However, the pharmaceutical study of Yejun Shen [4] et al. found that injection of osteoprotegerin has by-effects on the immune system. For example, if the patient has a bone tumor, osteoprotegerin can block the body's inhibition of cancer cells.

2.1.1.2 Anti-NF-κB receptor activation ligand antibody

Dinozumab belongs to the monoclonal antibody of NF-κB receptor activating ligand, and has no autoantibody. Its half-life and specificity are higher than that of osteoprotegerin. Juan Wang [5] et al. compared the effect of dinozumab and alendronate of postmenopausal OP women. The results showed that the BMD values of total hip and vertebrae were higher in the denosumab group than in the alendronate group after 6 months.

2.1.2 Cathepsin K inhibitor

Cathepsin K is a lysosomal cysteine protease that has specific procollagen activity for type I collagen and a high proteolytic activity and specificity for some extracellular matrix substrates. Both immunoblotting and immunocytochemistry studies confirmed that cathepsin K is expressed by osteoclasts and can be used as an ideal target. Inhibition of cathepsin K can achieve the effect of treating OP by inhibiting bone resorption. The first generation of cathepsin K inhibitor was balicatib (AAE-581). Studies have shown that [6] after 12 months of balicatib, postmenopausal women with lower bone density have BMD T values below -2.0, without bone formation markers reduction, the bone resorption marker decreased by 55-60%, and the total hip and vertebrae BMD increased by 2.2% and 4.4%, respectively. However, some patients had adverse reactions such as respiratory irritation and itching during medication, and the reason is related to balicatib belong to small molecule inhibitors of nitrogen-containing compounds, and it inhibits the activity of other cathepsins after accumulating in acidic organelles such as lysosomes. Odanacatib (MK-0822) belongs to the second generation of cathepsin K inhibitor, the study of Bone HG [7] et al. showed that after conducting

odanacatib treatment to postmenopausal OP patients, no obvious by-effects appeared during 24 months, after treatment, urinary N-terminal peptide and bone alkaline phosphatase decreased by 52%, 13%, total hip bone and BMD of the vertebrae increased by 3.2% and 5.5%, respectively. In the control group, the urinary N-terminal peptide decreased by 5% and the bone alkaline phosphatase increased by 3%, indicating that the inhibitory effect of Odanacatib on osteogenesis was less than the current anti-bone re-absorption of drugs.

2.1.3 Bisphosphonates

After being absorbed by the human body, the bisphosphonate can quickly enter the bone tissue and adsorb on the surface of the hydroxyapatite, inhibiting its dissolution, thereby inhibiting the energy metabolism of the osteoclast, inducing apoptosis or inactivation of osteoclasts, and slowing the bone transformation, so the bisphosphonate can be used alone as a bone resorption inhibitor for the treatment of OP. However, bisphosphonates have the disadvantages of low oral drug utilization and poor fat solubility. If large doses are given, nausea and vomiting may occur, while intravenous administration may cause local damage. In recent years, the binding use of anti-OP drugs such as estrogen, vitamin D and prostaglandins compound and bisphosphonates for the treatment of OP can solve the problem of many by-effects and poor selectivity of the original drug, for example, the linkage of bisphosphonate aminoethylidene diphosphonic acid with fullerene C60 improves fat solubility and bone-affinity property, realizing targeting drug use, thereby improving bioavailability, reducing dosage and by-effects.

2.2 Bone Synthesis Promoter.

2.2.1 PTH and PTHrP

Parathyroid hormone (PTH) is synthesized from the parathyroid hormone form in the parathyroid gland. The cell processing can transport a polypeptide wiyh 115 amino acids, which is assembled into mature PTH in the Golgi. The biological activity of PTH is mainly depend on the amino acid structure of 1-34 amino acids located at the end of N. The PTH is preceded by eight amino acids identical to the parathyroid hormone-related protein (PTHrP) in front of the N end, and the three-dimensional conformation of them in the 13-34 amino acid region is similar and can combine with PTH/PTHrP receptors, both of which have physiological functions that resisting thyrocalcitonin on hormones. PTH can reduce renal calcium excretion, but does not directly activate intestinal absorption of calcium, which firstly acts on osteoblasts, through regulation of osteogenic gene expression, and transmission of signals to osteoclasts by various cytokines secreted by osteogenic genes, for example, the interleukin family secreted by osteoblasts under PTH stimulation activates osteo-osteoblastic connections, activate osteoclasts. The bone targeting drugs currently used for clinical treatment of OP include recombinant human PTH1-34, the mechanism of which has not been completely clarified, and the pharmacodynamic effect is mediated by G-protein coupled receptors, which can change the activity of osteoclasts, bone cells and bones through multiple pathways. In addition, the fusion protein PTH-CBD composed of PTH1-33 and collagen CBN binding region can remain in the bone for a long time, which plays a role in sustained anabolism, similar to the activation of PTH1-34 to PTH/PTHrP receptor, but effective property and persistence is stronger than PTH1-34.

2.2.2 Barium ranelate

Barium ranelate can inhibit indirectly or directly mediate osteoclast activity and osteoclast differentiation, thereby inhibiting bone resorption and stimulating collagen and non-collagen synthesis and osteoprogenitor cell replication in osteoblasts and promoting bone formation, both in vitro and in vivo drugs have good tolerance, bioavailability and biological activity. The mechanism of barium ranelate is partially mediated by calcium-sensitive receptors, and short-term administration has the same effect as calcium-sensitive receptor agonists such as vitamin D3.

2.3 Tetracyclines.

Although tetracyclines have been used as broad-spectrum antibiotic in the past, their non-antibacterial effects are also obvious. The most prominent feature is that they can deposit in bone tissue and infiltrate into new bone. By artificially combining tetracyclines with anti-OP drugs such as estrogen, the selectivity of the drug can be improved, and the drug concentration can be located at the target to promote calcium deposition at the leading edge between mineralized bone and osteoid and increases local drug concentration, reduces dosing and adverse effects. At present, the method of compound linkage includes tetracycline and estrone linkage, tetracycline and estradiol coupling with succinyl, tetracycline and transforming growth factor a hydrophilic polyethylene glycol coupling etc. [8].

In addition to being used as a bone targeting drug carrier for the treatment of OP, tetracyclines have the unique advantage of promoting bone formation and inhibiting bone resorption, which can indirectly or directly affect bone metabolism, bone mass and bone structure, and not only reduce hormone-oriented bone damage, but can inhibit the induction of TNF-α by lipopolysaccharide and the tissue destruction of leukocyte-1β production, thereby preventing serious complications such as osteonecrosis.

3. Conclusion and Prospect

In summary, the current bone targeting drugs for the treatment of OP are mostly targeting at inhibiting bone resorption, by inhibiting the transformation of precursor osteoclasts into fully differentiated multinucleated cells, or by performing regulation of the rate of bone degradation in mature osteoclasts, thereby improving bone resorption, so many targeting drugs are focused on degrading bone matrix function and osteoclast differentiation, but promoting bone synthesis plays a decisive role in preventing and improving the prognosis of OP patients. Further studies on the molecular mechanisms of calcium-sensitive receptors, hormones, and specificity Wnt pathways may help to discover new osteoblast-specific targets, and the kinds of small molecule drugs will gradually increase, but many bone targeting drugs currently have by-effects and poor bioavailability problem, which leads to insignificant effects. In future studies, it may be considered to combine the target drugs with different mechanisms, connect them into a compound, or adopt a combination of traditional Chinese and Western medicine. Traditional Chinese medicines such as psoralen, nutmeg, morinda citrifolia, mulberry parasitic, and sichuan achyranthes are included in the research scope, thereby developing bone targeting drugs with better effects and lower by-effects.

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References

[1] Wantao Li, Qi Guo, Changjun Li, et al. A new approach to the treatment of osteoporosis: aptamer targeted delivery of drugs to reverse senile bone loss [J]. Progress in Pharmacy, 2017, 41 (10): 727-732.

[2] Matheson GO, Clement DB, Mckenzie DC, et al. Scintigraphic uptake of 99mTc at non-painful sites in athletes with stress fractures. The concept of bone strain. [J]. Sports Medicine, 1987, 4(1): 65-75.

[3] Chuncai Cui, Jing Wang, Yingxin Zhao, et al. Effects of nanomicelle composite PEG-PLL-OPG on osteoporosis and arteriosclerosis in mice[J] Journal of Practical Medicine,2016,32 (16) :2598-2602.

[4] Yingwei Shen, Xuebin Zhang, Lihong Wu, et al. Effect of recombinant human osteoprotegerin Fc fusion protein on early healing of osteoporotic fracture[J]. China Journal of Gerontology, 2016,

36 (10): 2327-2329.

[5] Juan Wang, Yu Yu, Qunbo Wang. Systematic evaluation of denosumab injection in the treatment of postmenopausal osteoporosis [J]. Chinese Journal of New Drugs and Clinical Remedies, 2013, 32(11): 885-891.

[6] Chappard D, Libouban H, Mindeholm L, et al. The cathepsin K inhibitor AAE581 induces morphological changes in osteoclasts of treated patients. [J]. Microsc Res Tech, 2010, 73(7): 726-732.

[7] Bone HG, Dempster DW, Eisman JA, et al. Odanacatib for the treatment of postmenopausal osteoporosis: development history and design and participant characteristics of LOFT, the Long-Term Odanacatib Fracture Trial [J]. Osteoporosis International, 2015, 26 (11): 2721-2721.

[8] Ping Zou, Yonghui Xie, Aiping Deng. Preparation and in vitro evaluation of tetracycline-mediated bone-targeted graft micelles[J]. Chinese Pharmaceutical Journal, 2017, 52(14): 1257-1262.