The Current Status of Sequential Therapy with Commonly Used Anti-Osteoporosis Drugs

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Abstract: As the trend of population aging intensifies, the incidence of osteoporosis is rising correspondingly. Osteoporotic fractures are one of the primary causes of disability and death in elderly patients, placing a great burden on both families and society in terms of medical care resources. The monotherapy of osteoporosis drugs has certain limitations and sequential drug treatment should be considered under the following circumstances: (i) when bone resorption inhibitors fail to work, have been used for too long, or cause adverse reactions; (ii) when the recommended treatment course of bone formation promoters (such as parathyroid hormone analogues) has ended but the patient's fracture risk remains high and requires continued treatment; (iii) when short-acting drugs such as teriparatide or denosumab need to maintain treatment effects after discontinuation. The sequential therapy of osteoporosis drugs can be categorized according to the mechanism of action into the following schemes: (i) bone formation promoters followed by bone resorption inhibitors; (ii) bone resorption inhibitors followed by bone formation promoters; (iii) different types of bone resorption inhibitors used sequentially; (iv) other sequential drug treatments. Osteoporosis is a progressive disease, and the ageing of the human population cannot be reversed. Therefore, single-drug treatment is unlikely to achieve the goal of long-term disease prevention and control, making the exploration of long-term treatment plans for existing drugs a key aspect of osteoporosis drug treatment.
***Keywords*:** osteoporosis, sequential therapy, anti-osteoporosis drugs

1. Background

Osteoporosis can lead to increased bone fragility and, consequently, an increased likelihood of fractures [1]. With the escalation of the aging population trend, the prevalence of osteoporosis continues to climb. Fragility fractures are one of the severe consequences of osteoporosis, and also one of the main causes of disability and death in the elderly [2-11]. The medical and nursing care burden of osteoporosis and fractures is a significant public health issue faced by our country.

However, the awareness, diagnosis, and treatment rates of osteoporosis are remarkably low among patients. In China, the awareness rate of osteoporosis patients over the age of 50 is 7%, the diagnosis rate is 36%, and only 6.5% of osteoporosis medications are being used for treatment [12-13]. This issue urgently requires attention. Currently, drug treatment is the main method for dealing with osteoporosis in clinical practice. Effective drug treatments can increase bone density and reduce the risk of fractures. Commonly used osteoporosis treatments include bone resorption inhibitors, bone formation promoters, dual-action drugs, and other mechanism-type drugs. Although the prevention and treatment of osteoporosis have made significant progress with the application of various anti-osteoporosis drugs, the choice of osteoporosis drugs and treatment strategies, the combination of drugs with different mechanisms, and sequential treatment plans are still being explored.

2. Current Status of Various Drug Treatments for Osteoporosis

2.1 Bisphosphonates

Bisphosphonate drugs include alendronate sodium, risedronate sodium, zoledronic acid, ibandronate sodium, and minodronate. They have shown significant therapeutic effects on both primary and secondary osteoporosis. A randomized controlled trial in postmenopausal women showed that compared with placebo, the minodronate group had a 59% lower risk of vertebral fracture (RR=0.41; 95%CI: 0.366-0.733)[14]. A randomized controlled trial involving 1199 male osteoporosis patients showed that compared with placebo, zoledronic acid significantly reduced the risk of new vertebral fractures (RR=0.33; 95%CI: 0.16~0.70)[15]. For patients with glucocorticoid-induced osteoporosis, bisphosphonates considerably reduce the risk of vertebral fractures (RR=0.57; 95%CI: 0.35~0.91)[16].

Common adverse reactions to oral bisphosphonates include abdominal pain, nausea, indigestion, and reflux. The most common adverse reactions to injectable bisphosphonates are fever, fatigue, chills, bone pain, joint pain, and muscle pain. For patients with renal impairment, renal function should be monitored before administration. It is contraindicated for patients

with a creatinine clearance rate <35ml/min. Rare adverse reactions include osteonecrosis of the jaw and atypical femoral fractures. Long-term bisphosphonate therapy may increase the risk of osteonecrosis of the jaw and atypical femoral fractures [17]. If an atypical femoral fracture occurs, medication should be immediately stopped.

2.2 Monoclonal Antibody Against Receptor Activator for Nuclear Factor κB Ligand (RANKL)

Currently, the only RANKL monoclonal antibody available is Denosumab. Denosumab significantly reduces the risk of new vertebral, non-vertebral, and hip fractures in patients with postmenopausal osteoporosis. Evidence suggests it can maintain its fracture risk reduction for up to 10 years and continuously improve bone mineral density without reaching a plateau[18-20]. Using Denosumab for 12 and 24 months in males with osteoporosis can significantly enhance bone mineral density [21]. For patients with glucocorticoid-induced osteoporosis, Denosumab can substantially improve the bone density of the lumbar spine and hip [22].

Patients with osteoporosis across different population groups have shown good tolerance to Denosumab [20, 21, 23-25]. The most common adverse reactions to Denosumab are musculoskeletal and limb pain. Rare cases include cellulitis, hypocalcemia, hypersensitivity reactions, osteonecrosis of the jaw, and atypical femoral fractures.

2.3 Parathyroid Hormone Analogues

Teriparatide is a recombinant human parathyroid hormone 1-34 fragment (rhPTH 1-34). Teriparatide has been proven to reduce vertebral and non-vertebral fractures in patients with postmenopausal osteoporosis [26]. Compared to bisphosphonates, Teriparatide can better mitigate the risk of vertebral fractures (RR=0.57; 95% CI: 0.35~0.93) and significantly increase the average percentage change in lumbar spine bone density at 6, 12, and 18 months [27]. Furthermore, compared to placebo, Teriparatide significantly reduces the risk of hip fractures [28,29]. A randomized controlled trial involving 437 adult male patients showed that 11 months of Teriparatide treatment can substantially increase the bone density of the lumbar spine and femoral neck [30]. For patients with glucocorticoid-induced osteoporosis, compared to the alendronate group, the use of Teriparatide can significantly enhance the bone density of the vertebrae and hip and significantly reduce the vertebral fracture rate.

Teriparatide has good overall safety, with common adverse reactions such as nausea, limb pain, headache, and dizziness. It is contraindicated in patients with hypercalcemia, metabolic bone diseases other than osteoporosis or osteogenesis imperfecta, severe kidney damage, malignant bone diseases, history of skeletal radiation, and pregnant or lactating women. After the injection of Teriparatide, the concentration of blood calcium may transiently slightly increase, or transient orthostatic hypotension may occur, which usually subsides in a short time and does not affect continued treatment. It is also not recommended for patients with an increased baseline risk of osteosarcoma [17,31,32].

2.4 Selective Estrogen Receptor Modulators (SERMs)

Selective estrogen receptor modulators, commonly used is raloxifene, have been shown in studies to reduce the risk of vertebral fractures in postmenopausal women by 40% (HR=0.60; 95%CI: 0.52~0.69) compared to the placebo group, but it has no significant effect on reducing the risk of hip or non-vertebral fractures [18]. Multicenter studies have found that, compared with the placebo group, raloxifene significantly increases the bone density of the spine, hip, and the whole body. After 24 months of medication, compared with placebo, daily oral raloxifene 60 mg increases the average bone density of the lumbar spine and hip by 2.4%, and the whole body average increases by 2% [33]. Raloxifene, in comparison to other drug regimens, does not show particular advantages in treating glucocorticoid-induced osteoporosis, and it may increase the potential risks of thrombosis, stroke, and cardiovascular events [34,35]. Therefore, it is only recommended for postmenopausal women with contraindications to all other treatment options.

Common adverse reactions to raloxifene include hot flashes, painful leg cramps, flu-like symptoms, and peripheral edema [32]. Furthermore, raloxifene may increase the risk of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism [36]. It is contraindicated in women with an active or previous history of venous thromboembolic events.

2.5 Monoclonal Antibody Against Sclerostin

Monoclonal antibody against sclerostin is currently refers to Romosozumab. Research has shown that romosozumab promotes new bone formation, inhibits bone resorption, and increases bone mass, trabecular bone, and cortical thickness for postmenopausal women. It significantly enhances bone density in the lumbar spine, total hip, and femoral neck, reducing the incidence of vertebral, non-vertebral, and clinical fractures; additionally, a decrease in the occurrence of falls has been observed [37,38]. Compared to the sole use of alendronate sodium, subsequent use of romosozumab significantly reduces the risk of fractures [39]. Clinical trials have also demonstrated that in male osteoporosis patients, using romosozumab for

12 months significantly increases the bone density of the total hip and femoral neck [40]. However, its use in patients with glucocorticoid-induced osteoporosis lacks clinical evidence.

Common adverse reactions to romosozumab include joint pain, headache, muscle spasms, peripheral edema, fatigue, neck pain, insomnia, and sensory abnormalities. Some patients may experience allergic reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria [41]. Major adverse cardiovascular events need attention [42,43]. Patients who have had a myocardial infarction or stroke in the previous year should not use romosozumab. If a patient experiences a myocardial infarction or stroke during treatment, romosozumab should be discontinued [39].

3. Sequential Therapy of Osteoporosis Drugs

The severity of osteoporosis, the attainment of therapy goals, and the response to failed treatments are crucial factors in determining the therapeutic sequence for individual patients[44]. Consideration for sequential drug therapy should be made in the following scenarios: (i)Ineffectiveness or adverse side effects of bone resorption inhibitors or prolonged therapy period; (ii)When the recommended treatment course of bone formation promotors such as parathyroid hormone analogues is completed, the fracture risk still remains high, thus requiring continued treatment; (iii)After discontinuation of short-acting drugs like teriparatide or denosumab, treatment needs to be maintained to sustain effects.

3.1 Sequential Treatment from Bone Formation Promoters to Bone Resorption Inhibitors

The sequential treatment from bone formation promotors to bone resorption inhibitors is widely recognized as a superior strategy in terms of mechanism and therapeutic effectiveness[45-52]. Clinical trial evidence has demonstrated that the sequential administration of teriparatide and denosumab can effectively improve bone mineral density (BMD) at various sites in postmenopausal women with severe osteoporosis [45], especially in lumbar spine and hip, with increases reaching as high as 18.3% and 6.6%, respectively, more than that in denosumab sequential teriparatide therapy [46]. Sequential administration of teriparatide with bisphosphonates [47,48] or denosumab [49,50] both resulted in further increases in bone density, with the increases in the lumbar spine, hip, and femoral neck BMD in patients receiving teriparatide followed by denosumab higher than those in patients receiving teriparatide followed by oral bisphosphonates (lumbar spine: 6.2% vs 2.6%, hip: 4.2% vs 1.1%, femoral neck: 3.5% vs 1.4%). Another study indicated that compared with sequential denosumab, sequential bisphosphonates (including alendronate, risedronate, ibandronate, and zoledronate) following teriparatide resulted in a more significant increase in vertebral BMD (0.1% vs 3.7%, P=0.003) [51]. After teriparatide followed by raloxifene treatment, after 2 years, vertebral BMD was maintained, and total hip and femoral neck BMD significantly improved, suggesting that teriparatide followed by raloxifene has a certain enhancing effect on hip BMD [52].

3.2 Sequential Treatment from Bone Resorption Inhibitors to Bone Formation Promoters

Several studies have shown that switching to teriparatide after bisphosphonate treatment significantly reduces hip BMD, with varying degrees likely due to bisphosphonates binding to hydroxyapatite[53]. However, other studies suggest that patients who have previously received alendronate, risedronate, etidronate can significantly increase their lumbar and hip BMD after 2 years of sequential teriparatide treatment[54]. After denosumab, a short-term (6-month) decline in lumbar spine BMD and a continuous decline in hip and femoral neck BMD within 1 year were observed, but after that, BMD gradually increased[45]. After either raloxifene or alendronate was followed by teriparatide, the lumbar spine BMD in the raloxifene group increased by 10.2% after 18 months, while the alendronate group increased by only 4.1%[55]. Thus, teriparatide could be considered for continued treatment after raloxifene. Due to the possible temporary decrease in BMD when switching from bone resorption inhibitors to bone formation promotors, this is not considered the primarily recommended treatment plan.

3.3 Sequential Treatment of Different Types of Bone Resorption Inhibitors

Bone resorption inhibitors are the most commonly used drugs for clinically treating osteoporosis. If a patient fails to achieve treatment goals or experiences adverse reactions after using a particular drug, it is necessary to switch to another bone resorption inhibitor. After 1 year of alendronate following denosumab, there was a slight increase in BMD[56]. In the case of zoledronic acid following denosumab, there was a decrease in BMD in the first year, but BMD was maintained in the second year[57,58]. Another study found that, in patients treated with zoledronic acid following denosumab, both the lumbar spine and femoral neck BMD increased significantly at 6 or 12 months[59]. In patients treated with raloxifene after denosumab for 12 months, there was some decrease in BMD, but the decrease was less than that seen in the no-medication group[60]. Moreover, another study suggested that after 1-2.5 years of denosumab treatment, sequential treatment with Raloxifene for 12 months can restore bone density to baseline [61]. Therefore, denosumab followed by bisphosphonates can extend benefits to a certain extent, while the benefits of following raloxifene are limited.

3.4 Sequential Treatment of Other Drugs

After romosozumab followed by two years of denosumab, the increase in bone density is more significant than with zoledronic acid, especially in the lumbar spine (increases of 19.9% and 17.9%, respectively) [63]. Following 12 months of treatment with romosozumab, followed by 12 months of treatment with alendronate sodium, compared to 24 months of treatment with alendronate sodium alone, the risks of vertebral, non-vertebral, and hip fractures were reduced by 48%, 20%, and 38%, respectively [40]. Postmenopausal women with osteoporosis who used romosozumab followed by a bone resorption inhibitor had a greater increase in bone density than those using a bone resorption inhibitor alone [64]. For postmenopausal women with low bone mass, under the treatment plan of 24 months of romosozumab followed by 12 months of denosumab, followed by 12 months of romosozumab, the bone density of the total hip and lumbar spine further increased in the third stage of treatment.

4. Conclusion

Over the past 30 years, the development of new therapies for osteoporosis has been continuously promoted. We now have potent interventions that can both reduce bone resorption and increase bone formation. However, the pace of therapeutic development has significantly slowed down, and there are currently no new anti-osteoporosis drugs in advanced clinical trials. Therefore, the current research agenda needs to shift to how to optimally use available drugs to treat individuals at risk of fractures. More large-scale, fracture endpoint-based randomized controlled trials are still needed for the treatment of osteoporosis, to promote personalized precision medicine for osteoporosis patients, and to compare the effectiveness and safety of different drug treatment regimens.

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