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Sequential osteoporosis treatments

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ABSTRACT

Osteoporosis is a major public health concern due both to its high prevalence and to its association with potentially serious fractures. The chronic nature of osteoporosis, together with the aging of the population, may result in a need for prolonged treatment consisting in the sequential use of several osteoporosis drugs. Situations in which switching from one osteoporosis drug to another may be considered include the occurrence of a fracture despite treatment, poor treatment adherence, side effects, and completion of a first-line treatment course. The available recommendations for postmenopausal women deal only with the indications for first-line osteoporosis treatment. Studies on drug sequences used an open-label design and failed to collect data on fractures. Thus, there is no scientific evidence supporting a specific treatment sequence, the only exception being teriparatide followed by a bone resorption inhibitor. Consequently, selection of the second drug in an osteoporotic woman is a matter of clinical judgment, which can be guided by several factors such as health insurance reimbursement restrictions, characteristics of the osteoporosis (e.g., severity and whether there is a predominant risk of peripheral fractures), co-morbidities, contraindications to specific drugs, and patient adherence to prescriptions.

Osteoporosis is a major public health concern due both to its high prevalence and to its association with potentially serious fractures. Currently available osteoporosis medications diminish the fracture risk by 15% to 70% depending on the drug and type of fracture. Osteoporosis medications fall into three groups:

- bone resorption inhibitors (bisphosphonates, selective estrogen receptor modulators [raloxifene], menopausal hormone replacement therapy, and denosumab);
- a bone formation enhancer (PTH 1-34 [teriparatide]);
- strontium ranelate, whose effect is mixed.

The chronic nature of osteoporosis, together with the aging of the population, may result in a need for prolonged treatment consisting in the sequential use of several osteoporosis drugs. The main issues are definition of the situations that may require sequential therapy and selection of the best drug sequences.

1. Situations that may require sequential therapy

1.1. Fracture despite treatment

In clinical trials, osteoporosis medications diminished the fracture risk by 30% to 70% at the spine and by 16% to 53% at other sites. None of the treatments eliminated the fractures completely. If a fracture occurring despite treatment indicates a treatment failure, then switching to another medication is warranted. However, several points must be checked before concluding that the current medication is not effective:

- is the fracture related to bone fragility? Fragility fractures occur for trivial injuries (e.g., falling from the standing position) at sites consistent with osteoporosis (not at the skull, cervical spine, or digits);
- is the fracture related to postmenopausal osteoporosis? Even in a woman with a known history of osteoporosis, investigations must be done to rule out a primary tumor, myeloma, and causes of secondary osteoporosis;
- did the patient take the treatment as prescribed (in terms of both persistence and adherence)?;
- is the calcium and vitamin D intake adequate?;
- was the interval from treatment initiation to fracture occurrence longer than the time needed for the drug to take effect (6 to 18 months depending on the drug)? Fractures occurring earlier do not warrant a change in treatment.

1.2. Poor patient adherence

Oral osteoporosis treatments are characterized by poor persistence and adherence, for several reasons: osteoporosis is asymptomatic until a fracture occurs, the patient may be unconvinced that the treatment is effective, the treatment modalities

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are often perceived as burdensome, and concern about side effects may lead the patient to question the risk/benefit ratio. A literature review on bisphosphonates in postmenopausal osteoporosis showed that persistence after 1 year was better with weekly dosing (49.6%–69.5%) than with daily dosing (31.7–55.7%) [1]. In a French study of the Thalès database, 1-year persistence in patients taking oral bisphosphonates was 47.5% with ibandronate and 30.4% with weekly bisphosphonates [2]. These studies suggest that, although persistence may be better with monthly dosing than with shorter dosing intervals, it remains low. No data are available on persistence with yearly 5-mg zoledronic acid infusions. However, a study showed that patients were more likely to prefer yearly zoledronic acid infusions over weekly bisphosphonate dosing (66.4%–78.8% vs. 9%–19.7%) [1]. It is reasonable to assume that failure to take a medication as prescribed will lead to decreased effectiveness. A study of a Canadian cohort of 11,249 women treated for postmenopausal osteoporosis showed good treatment adherence and persistence in half the cases after 2 years [3]. After adjustment on other fracture risk factors, good adherence and persistence were associated with significantly fewer fractures. The difference in terms of fracture incidence was 25.4%/100 patient-years ($P < 0.0001$) [3]. In the observational study ICARO (Incidence and characterization of inadequate clinical responders in osteoporosis), factors associated with an inadequate response to bone resorption inhibitors were poor adherence (below 50%) and absence of calcium and vitamin D supplementation [4].

1.3. Adverse effects

The occurrence of adverse events is among the main reasons for discontinuing osteoporosis medications. In an Italian cohort study of 9851 postmenopausal women given calcium and vitamin D supplements or hormone replacement therapy or raloxifene or bisphosphonates on a daily or weekly basis, the main reasons for treatment discontinuation within the first year were the occurrence of adverse events and concern about possible adverse events [5].

1.4. At completion of the first course of osteoporosis treatment

In controlled trials, osteoporosis medications were shown to reduce the fracture risk for 3 to 5 years, the only exception being teriparatide, which was evaluated for only 2 years. Data are now available for longer periods: 10 years with alendronate [6,7], 7 with risedronate [8], 10 with strontium ranelate [9], 8 with raloxifene [10], and 6 with zoledronic acid [11]. After 5 years of osteoporosis treatment, the appropriateness of further treatment should be evaluated. Continued treatment beyond 5 years is probably in order in women with any of the following: severe fracture at baseline (i.e., fracture involving the proximal femur, spine, proximal humerus, distal femur, tibia, pelvis, or three adjacent ribs) [12], fracture during treatment, development of new risk factors, significant bone mineral density (BMD) decline ($\geq 0.03\ g/cm^2$) at the spine or hip [13], and/or persistently low T-score values (≤ -3). In some cases, it may be appropriate to switch to another osteoporosis drug instead of continuing the same treatment.

2. Published data on osteoporosis drug sequences

Osteoporosis medications differ regarding the main sites at which they decrease the fracture risk (vertebras, hip, or all non-vertebral sites). Clinical trials showed a decrease in the fracture risk decrease in osteoporotic postmenopausal women with or without fractures who were naive to osteoporosis medications. Most of the studies of sequential treatments involved first-line bisphosphonate therapy, whose carry-over effect after intake discontinuation may have influenced the effects measured during the second-line treatment. The efficacy endpoints in these studies were BMD values and bone remodeling markers. No data were obtained on the fracture rates.

2.1. A second bisphosphonate after a first bisphosphonate

A multicenter double-blind randomized trial compared the BMD effects of a zoledronic acid infusion versus continued alendronate therapy in 225 women with low BMD values (T-score ≤ -2 before alendronate therapy). All patients started by taking alendronate 70 mg/week for at least 1 year (mean: 4 years). The lumbar spine BMD gain after 1 year was comparable with zoledronic acid (+0.16%) and alendronate (0.8%). Compared to baseline, the bone resorption marker values remained unchanged in the alendronate group and dipped significantly after 3 months in the zoledronic acid group then increased while remaining lower than in the alendronate group after 1 year [14]. This study suggests that switching from alendronate to zoledronic acid may fail to improve BMD values after 1 year. No information is available on this sequence in patients with an inadequate response to oral bisphosphonate therapy.

2.2. Second-line strontium ranelate after bisphosphonate therapy

Strontium ranelate both increases bone formation and inhibits bone resorption. Strontium ranelate was effective in preventing fractures in women naive to osteoporosis medications. The carry-over effect of bisphosphonates after treatment discontinuation may, in theory, decrease the efficacy of strontium ranelate by inhibiting the incorporation of the drug into newly formed bone. In addition, studies have shown a decreased response to teriparatide in patients previously given alendronate.

2.2.1. Effects on bone mineral density

In an open-label study in the UK, the BMD effects of strontium ranelate were evaluated in 120 osteoporotic postmenopausal women, including 60 who were naive to osteoporosis medications and 60 who had taken bisphosphonate therapy [15,16]. In this last group, bisphosphonate therapy was stopped because of an inadequate response (lumbar spine BMD loss $\geq 2.7\%$ despite good treatment adherence) or an adverse event. In the treatment-naive group, BMD gains after 1 year were significant at the lumbar spine (+5.6%, $0.047\ g/cm^2$, $P < 0.001$) and total hip (+3.4%, $0.027\ g/cm^2$, $P < 0.001$) and were comparable to those obtained in Phase III trials of strontium ranelate. In the prior-bisphosphonate group, the BMD gain was significant only at the lumbar spine (+2.1%, $0.017\ g/cm^2$, $P = 0.002$) and not at the total hip. After 1 year, the BMD changes at the lumbar spine and total hip were significantly greater in the bisphosphonate-naive group than in the prior-bisphosphonate group. After 2 years, the BMD gains at the lumbar spine were similar in the two groups, except during the first 6 months, when the response was blunted in the prior-bisphosphonate group. At the hip, the BMD gain after 2 years was significant in both groups but smaller in the prior-bisphosphonate group than in the bisphosphonate-naive group [15,16]. The authors of these two studies suggest that persistent bone turnover inhibition after bisphosphonate discontinuation may prevent the incorporation of strontium ranelate into new bone and that the anabolic effect of strontium ranelate may be blunted in bisphosphonate-exposed individuals.

2.2.2. Effects on bone turnover markers

In the above-mentioned study [15], in the group previously exposed to bisphosphonates, the markers for bone resorption (serum CTX) and formation (PINP and bone alkaline phosphatase)