

Sequential therapy and stratified risk of osteoporotic fracture

Osteoporosis is a chronic disease defined by a reduction in bone strength that predisposes individuals to fractures. The risk of fracture determines the indication for treatment. This risk is not constant but rather changes throughout life depending on associated comorbidities and the nonpharmacological and pharmacological measures that are implemented (1).

The therapeutic armamentarium available for the treatment of osteoporosis is broad, with the primary objective of reducing the number of fractures while maintaining acceptable adverse effects in relation to the benefit obtained. On the other hand, antiosteoporotic drugs have a limited duration of effect, either due to regulatory agency restrictions, decreased efficacy over time, or serious adverse effects, whereas the duration of the disease itself is prolonged. Moreover, most of these drugs, with the exception of bisphosphonates, have transient effects, losing their benefit once treatment is discontinued. This necessitates the use of sequential therapy (2), which consists of the successive use of different drugs in order to maintain their effectiveness. The sequence employed is determined by fracture risk and the individual clinical situation of each patient. Of note, osteoporosis treatment is long-term and may last throughout the patient's lifetime, depending on the persistence of fracture risk (3).

Numerous factors determine fracture risk, but to establish risk groups, different clinical guidelines have used age, prior fracture, and bone mineral density (BMD) (4,5). Age is a key factor, as for similar BMD values, fracture risk increases with age, and the incidence of different fracture types changes: distal radius fractures are more prevalent in younger women, whereas vertebral and hip fractures predominate in older populations (6). Although a high proportion of fractures occur in individuals with BMD values in the osteopenic range, BMD—particularly at the hip—is a determinant of fracture risk. This was recently confirmed by the SABRE study, which included data from more than 50 clinical trials encompassing 50 000 fractures (7). Probably the most influential factor is a prior fracture, which increases the risk of new fractures, especially during the first two years after the initial fracture, although the risk persists throughout the patient's lifetime (3,5). A study conducted in our health area, including 276 postmenopausal women followed for eight years and analyzed using machine learning techniques, showed that prior fracture was the variable with the greatest weight in fracture risk; these data were validated in a general population cohort (8). Based on these findings, SEIOMM established three risk categories: moderate, high, and very high (4). The position of ASBMR-BHOF is similar, taking into account the presence or absence of fractures, the time elapsed since fracture, and fracture location (5).

In patients at moderate risk, initial therapy with a selective estrogen receptor modulator (SERM) is recommended; however, age modifies risk, and treatment should subsequently be continued with a drug that reduces hip fracture risk, such as bisphosphonates or denosumab (1). Patients at high risk modify their initial therapy depending on three situations: intolerance to oral bisphosphonates, duration of previous therapy, and treatment failure (9). In the first situation, continuation with a parenteral antiresorptive agent—zoledronate or denosumab—is recommended, achieving a reduction in bone remodeling and an increase in BMD. Bisphosphonates show greater efficiency during the first five years; beyond this period, they maintain bone mass but do not increase it, although their antifracture efficacy likely persists for up to ten years (10). Parenteral zoledronate maintains this benefit when used for six years, whereas denosumab produces a continuous increase in bone mass; however, after ten years, data on fractures and safety are lacking (2). Of note, the baseline hip T-score when selecting therapy, as the likelihood of achieving a T-score > -2.5 varies depending on the drug used. In this group, the presence of treatment failure shifts the patient into the very high-risk category and should be managed accordingly.

A special situation in sequential therapy arises after denosumab discontinuation, to avoid the development of multiple fractures. A bisphosphonate should be used—oral for treatment durations shorter than two and a half years (11) or intravenous zoledronate for longer periods (12). Real-world studies have shown the benefit of zoledronate in preventing multiple fractures. An anabolic agent should not be used in this context, as it would increase bone remodeling and thereby raise the risk of multiple fractures.

Patients at very high risk require initial sequential therapy with an anabolic or dual agent (teriparatide, abaloparatide, or romosozumab), followed by an antiresorptive drug. In treatment-naïve patients, a clear benefit is observed

compared with monotherapy, whereas in patients previously treated with antiresorptives, the densitometric response is partially blunted, although antifracture efficacy is not diminished (13,14). Among the available anabolic agents, only romosozumab can be used in a subsequent cycle; this is not possible with teriparatide or abaloparatide. With any type of sequential therapy, regardless of patient risk, the final drug in the treatment sequence is a bisphosphonate (10).

In conclusion, sequential therapy is effective in reducing osteoporotic fractures, and the therapeutic regimen should be individualized according to fracture risk, comorbidities, and the patient's clinical situation.

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