Revista de Osteoporosis y Metabolismo Mineral
ISSN: 1889-836X
ISSN: 2173-2345
Sociedad Española de Investigaciones Óseas y Metabolismo Mineral

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Revista de Osteoporosis y Metabolismo Mineral, vol. 14, no. 1, 2022, , pp. 3-4
Sociedad Española de Investigaciones Óseas y Metabolismo Mineral

DOI: https://doi.org/10.4321/S1889-836X2022000100001

Available in: https://www.redalyc.org/articulo.oa?id=360972500001

Rev Osteoporos Metab Miner. 2022;14(1):3-4

Towards an individualised approach to management of osteoporosis

DOI: http://dx.doi.org/10.4321/S1889-836X2022000100001

Bente L Langdahl
Professor, MD, PhD, DMSc, Department of Endocrinology and Internal Medicine, Aarhus University Hospital and Institute of Clinical Medicine, Aarhus University (Denmark)

The treatment and management of osteoporosis, like any other disease, should be evidence-based in order to give the patients the best chance of limiting the consequences of the disease. Osteoporosis is a very common condition, affecting more women than men, and often overlooked and undertreated. The updated clinical practice guideline on postmenopausal, glucocorticoid induced, and male osteoporosis from the Spanish Society for Bone and Mineral Metabolism Investigation (SEIOMM)[1] is an important tool for clinicians with respect to diagnosis, future fracture risk assessment, and treatment of osteoporosis.

The diagnostic criteria are based on DXA and the presence of fractures, the criteria are not new, but the emphasis on recent fractures is new and worth noticing. A patient with a prior major osteoporotic fracture has a higher risk of fracture than a person at the same age without a fracture for up to 10 years following the first fracture, however, the risk in the 2 years immediately following the fracture is several times higher[2]. Therefore, the period following a fracture is a window of opportunity for prevention of the next fracture. The Fracture Liaison Service concept was developed to reduce the worldwide gap in fracture patients being assessed for osteoporosis.

The concept was developed more than 2 decades ago and although being implemented at a variable rate around the world, more and more evidence seems to suggest that the concept of systematically investigating fracture patients for osteoporosis is a cost-effective approach by reducing the risk of the next fracture[3].

The guideline divides postmenopausal women with osteoporosis into three risk categories based on a combination of prevalence of fractures, BMD and clinical risk factors. The three risk categories are well defined and leave room for an individualized assessment of fracture risk, however, the important concept of imminent fracture risk is not incorporated in the algorithm. There is always a balance between keeping such algorithms simple and providing the needed information, but in this case an arrow from the high risk group to the very high risk group in the case of a recent fracture could easily have indicated this association between a recent fracture and a higher fracture risk.

There is an increasing amount of evidence supporting the recommendation of using bone anabolic treatments; teriparatide or romosozumab in women at high risk of fracture. The VERO trial clearly showed that teriparatide is superior to risedronate in preventing vertebral and clinical fractures in women at high risk of fracture[4]. Similarly, the ARCH trial demonstrated that romosozumab for 12 months followed by alendronate is superior to alendronate in preventing vertebral, clinical, non-vertebral and hip fractures in women with severe osteoporosis[5]. In addition, there is also evidence to suggest a greater benefit on BMD improvement when using bone anabolic treatment before an antiresorptive, compared to the reverse sequence[6,7]. Although the discussion about a treatment target in the individual patient is still ongoing, the work of the FNIH Bone Quality working group has clearly shown that BMD and increase in BMD in response to treatment are important predictors of future fracture risk[8]. It is therefore important to improve BMD as much as possible, especially, in patients at high or very high risk of fracture.

The moderate risk group comprises the largest number of patients and considering the low grade of evidence for an anti-fracture effect of the SERMs it is somewhat surprising to see SERMs being the first choice of treatment in this group of patients. The evidence from the clinical trials investigating the more potent bisphosphonates; alendronate, risedronate and zoledronate and denosumab have demonstrated that these treatments are effective and reduce vertebral as well as non-vertebral fractures in postmenopausal women with osteoporosis. In addition, these treatments will increase BMD more than the SERMs and for the bisphosphonates allow for periods of treatment interruption.

This updated guideline leaves behind the strategy that one treatment, typically oral bisphosphonate and one regimen, typically oral bisphosphonate for 5 years are the best for all patients. The updated guideline has a very clear individualized approach to the choice of initial treatment as well as long-term management of osteoporosis. The long-term management algorithm is less evidence based due to the lack of well conducted clinical trials investigating the long-term management of osteoporosis. The recommendations for treatment duration of SERMs and denosumab are based solely on the duration of the clinical trials performed and the lack of information about beneficial effects and adverse effects thereafter. The suggested treatment durations for bisphosphonates are based on small studies on treatment discontinuation. This approach to defining treatment duration is clearly different from most other medical diseases and treatments. Although most studies of treatment of hypertension and diabetes have a duration of a few years, it is not recommended to discontinue these treatments after a few years in clinical practice. The increasing risk of rare adverse effects like osteonecrosis of the jaw and atypical femur fracture with increasing treatment duration should be taken into account and the benefit-risk balance considered individually in every patient; however, the benefit-risk balance was very clearly positive after 10 years with denosumab in the FREEDOM trial[9] as the incidence of these rare adverse effects was very low. It is difficult to imagine that the benefit-risk balance would change dramatically in the following years, if the patient is still at risk of fractures.

Bisphosphonates are the exception among the available osteoporosis treatments as bisphosphonates are accumulated in bone during treatment and therefore the anti-fracture effect seems to be preserved with respect to non-vertebral fractures if the patient is at low-to-moderate risk of fracture determined by a combination of treatment duration, fracture history and BMD.

The difficult aspect of treatment interruption is not determining which patients fulfill the criteria developed on the basis of the FLEX and the HORIZON trials, but how to monitor and manage the patients interrupting treatments. It is also not clear if temporary treatment interruption of 1-2 years followed by reinitiating of the treatment affects the risk of the rare adverse effects long term.

The updated guideline recommends treatment specific fixed periods of interruption. This seems to be a good approach as it has been demonstrated that the response in terms of change in bone turnover markers and BMD after discontinuation is highly variable[10]. However, this strategy also raises some questions that are currently unanswered; first, does this strategy of short term interruption of treatment leads to more than a temporary reduction in the risk of the rare adverse effects; second, how many patients and doctors lose track of the treatment strategy and treatment is therefore not reinitiated, and third, some patients seem to have stable BMD and low levels of bone turnover markers for years after treatment interruption, do they need reinitiating or could they stay without treatment for a longer period of time?

One aspect of osteoporosis management that is not mentioned in the summary of the updated guideline is patient education, engagement and empowerment. This is an important aspect of long-term management of osteoporosis treatment. Patients who understand what osteoporosis is, how osteoporosis affects their future risk of fractures, and how this risk can be reduced by medical treatment, physical activity and training, and a healthy lifestyle are more likely to remain compliant with treatment and be able cope with having a chronic disease that may imply changes to daily living and activities[11].

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