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Sequential treatment: it has come a long way... with a long way to go

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Innovations in therapeutic behavior in the face of a certain disease are generally designed to improve effectiveness. But sometimes they may have other reasons. For example, avoiding side effects, lowering the cost or making the form of administration of a drug more comfortable. Sequential therapy represents a therapeutic innovation in the field of osteoporosis.

The first form of sequential therapy used in osteoporosis was probably called ADFR (A = activate remodeling, D = depress resorption, F = free formation, and R = repeat) or "coherence therapy", initially proposed by Frost around 1980[1]. The theoretical approach on which this strategy was based was to synchronize the remodeling units, placing them in the spring phase, by administering an osteoclast-stimulating drug, to then inhibit them. Afterwards, a free time of 2-3 months was left, during which the osteoblasts, activated by the coupling set in motion with the initial stimulus of the osteoclasts, were supposed to develop the osteoforming effect. The ADFR regimen was a therapeutic innovation that was intended to improve the efficacy of osteoporosis treatment, but it was a failed attempt.

The next form of sequential treatment that was considered in osteoporosis did so much later, some 20-25 years later. And, unlike the ADFR guideline, it was not established as a consequence of a theoretical reasoning, but arose as a necessity when it was found that the suspension of the administration of teriparatide was followed by a loss of the effects achieved with it, unless that an antiresorptive drug was administered[2]. It was therefore a regimen that we previously described as intended to improve therapeutic efficacy.

Sequential therapy can also be applied in the field of osteoporosis to avoid side effects. In fact, the knowledge that prolonged treatment with potent antiresorptives (bisphosphonates, denosumab) can lead to serious complications, such as atypical femoral fracture (AFF) and osteonecrosis of the jaws, has led to at least two forms of sequential therapy in the management of the disease. One of them, only applicable to relatively young women (50-60 years) with mild-moderate osteoporosis that does not involve a risk of hip fracture, consists of administering during the first 6-8 years (depending on the age of the patient) a SERM, so that bisphosphonates or denosumab can be introduced later, and the patient can delay her exposure to the risk of the aforementioned complications[3]. The other affects those patients who are already under treatment with these drugs, and have been doing so for at least five years before. In them, the possibility of stopping the drug (specifically in the case of bisphosphonates) should be considered, since it is known that this reduces the risk of AFF rapidly. The risk-benefit ratio must first be assessed. If bisphosphonate is discontinued, the risk of FAF decreases, but that of osteoporotic fracture increases. When this is small, the risk can be assumed. Withdrawal of the drug then places the patient on what we call "therapeutic holidays"[4]. After these, the drug should be reintroduced, to return, perhaps, in the future to a new holiday period (bisphosphonate-holiday-bisphosphonate-holiday cycles, etc., with which the patient could remain adequately treated for the rest of his life). If the risk of osteoporotic fracture is great, what should be done, instead of suspending the treatment, is to administer a drug that does not carry the risk of the complications referred to: specifically, teriparatide (which Nelson Watts, in some ASBMR webinars, has called very graphically "sabbatical period", establishing an analogy with drug holidays). Both the sequence bisphosphonates-drug holidays-bisphosphonates, etc., and the sequence bisphosphonates-teriparatide-bisphosphonates, are two good examples of sequential treatments aimed at avoiding complications. Discussing the extent to which the concept of therapeutic vacation could be applied to denosumab and that of sabbatical to romosozumab requires comments beyond the scope of this editorial.

Another reason that may motivate a change in osteoporosis treatment is perception, when assessing patient evolution. Response is inadequate and a change should be made (it may be debatable whether by changing drug the concept of "sequential therapy" is appropriate –in other pathology fields it would not be considered this way–; however, for the purposes of our discussion here, we can accept it). In such a case, the reported[5] attitude could consist of one of these three possibilities: a) changing the drug considered insufficiently effective for another of the same, more potent type; b) change from an oral drug to an injectable one; c) change from an antiresorptive to an osteoformer. Today we might add, for certain occasions, a fourth possibility: the combination of two drugs, generally an osteoformer and an antiresorptive. Imagine, for example, a therapeutic failure of denosumab in a situation where, due to lack of availability or due to contraindication, romosozumab cannot be used since the administration of teriparatide after denosumab is not recommended. It could be switched to an association of teriparatide with zoledronate or even with denosumab itself. The combination, therefore, can constitute one more link in the therapeutic chain of sequential treatment.

The possible sequential guidelines for the treatment of osteoporosis are numerous. Fortunately, almost all of them have been studied and, consequently, we have a lot of information about them. But precisely their high number and the occasional existence of discrepancies in their results, require, in order to facilitate their knowledge, to carry out a necessarily laborious task of systematization and analysis. And this is exactly the task carried out by Drs. Casado and Neyro in the article published in this issue of the journal[6], facilitating our work in such a complex field.

The therapeutic sequences considered in this article constitute a sound basis on which to decide which specific treatment guidelines are appropriate. In some cases, the information we already have will suffice. But at other times, new studies will be needed to supplement the ones that have existed so far. The latter will occur, for example, when the current data come from studies whose outcome variables are not fractures, but others of a surrogate nature (in general, bone mineral density [BMD]). Or when it is necessary to include aspects not previously considered in the regimen in question, such as economics or those related to the convenience of drug administration.

There are multiple examples. The administration of denosumab after a bisphosphonate increases BMD more, but we lack data regarding the effect that this has on reducing fractures (this idea of reaching a certain BMD value –more specifically the T-index– responds to a concept that is very attractive –that of the "treat-to-target"–, which may possibly play an interesting role in the future, but which is currently not mature enough). In this regard, some authors[7,8] have recently insisted on the similarity of the efficacy of zoledronate and denosumab in reducing the risk of fractures despite the greater effect of the latter on BMD. Osteoformers have been shown to be more effective than oral antiresorptives, but we do not know what would happen if they were compared with denosumab or zoledronate. Starting a treatment with an osteoformer to continue with an antiresorptive may be more effective than starting with the antiresorptive directly when the risk of fracture is very high. It has not been proven, however, that the same occurs when the risk is not so high. Incidentally, it is striking that authors who defend that this guideline is used in a practically generalized way, explicitly indicate in their published findings that this proposal does not take into account economic aspects and the convenient use of the osteoformer[9,10]. Administering cycles of a bone-forming drug separated by that of an antiresorptive has also been considered a particularly effective osteoporosis treatment. The administration of two osteoformers in succession, one after the other, has even been suggested. Again, they are examples of suggestive theoretical approaches pending evaluation in practice both from the point of view of their efficacy and their viability (cost or acceptance by the patient).

Thus, sequential treatment, with its various modalities, represents a clear advance in the management of osteoporosis. The possibilities are numerous, but there are still aspects to be clarified. Experience with the ADFR regimen teaches us to be prudent in accepting therapeutic innovations. Reviews such as the one published by Drs. Casado and Neyro help us to proceed in a field that is becoming increasingly complex. We need to know how to distinguish what is already proven from what is not beyond mere speculation.

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