Endorsed by AME
Italian Association of Clinical Endocrinologists
ITALIAN CHAPTER
www.aaceitalianchapter.com
Endocrine News
10-2018

Management of the osteoporotic patient with poor response to treatment

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Osteoporosis treatment may reduce but not eliminate the risk of fracture, which is why a fragility fracture during treatment does not necessarily imply therapeutic failure and the need to modify therapy. The precise definition of a «poor responder», and its management, remain a source of debate.

A patient is considered a «good responder» when, after at least a year of treatment:

- Does not experience a new clinical or radiological fracture
- Shows a significant increase in bone mineral density (BMD) and a favorable evolution of the indexes of skeletal turn-over (a reduction if on anti-absorptive treatment, an increase if on anabolic treatment).

If either of these conditions is not met after at least 1 year of appropriate treatment, it is important:

- To verify adherence to the osteoporotic treatment and to the oral supplementation of calcium and vitamin D, keeping in mind that the efficacy of osteoporotic medications has been confirmed only in patients who adhere to the therapy and maintain an adequate intake of calcium and vitamin D. **Poor adherence to treatment, or inadequate supplementation of calcium and vitamin D, represent the most common causes of therapeutic failure**.
- To look for a secondary cause of osteoporosis: in these patients, while response to osteoporosis treatment may be suboptimal, therapy directed to the underlying cause may also have positive skeletal repercussions.

Having verified these two points, the 2012 guidelines of the International Osteoporosis Foundation recommend modifying treatment in the following circumstances:

- ≥2 new fragility fractures
- A new fracture associated to a significant decrease in BMD and/or lack of a substantial reduction of the indexes of skeletal turn-over (in the event of anti-absorptive treatment)
- A significant decrease in BMD together with lack of reduction of the indexes of skeletal turn-over (in the event of anti-absorptive treatment).

Despite the scarcity of evidence, Diez-Perez et al provide the following advice for the management of a patient with a poor response:

- To replace an anti-absorptive drug with a stronger one of the same class
- To replace an oral treatment with a parenteral treatment
- To replace a strong anti-absorptive drug with an anabolic one

Obviously, the recommendations assume that the initial choice of medication was appropriate to the type of fracture experienced by the patient. From a «treat-to-target» perspective, the Italian medicine evaluation agency (AIFA) has produced a document (AIFA 79) which stratifies pharmacological treatment of osteoporosis in 3 levels, according to the risk factors of each patient. This document, less conservative than the report of the International Osteoporosis Foundation, suggests transition to the next pharmacological level in any patient on treatment for at least 1 year who experiences a new vertebral or femoral fracture. As recent evidence suggests, caution is required in applying this sequential treatment, since current data are limited by use of surrogate rather than clinical end-points (i.e. BMD rather than fracture), lack of specific focus on non-responders, and high heterogeneity in the definition of response. It is possible, however, to draw the following conclusions.

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Bisphosphonates → Denosumab: ✓
Denosumab inhibits bone reabsorption more than oral bisphosphonates. The transition from an oral bisphosphonate (Alendronate, Risedronate or Ibandronate) to Denosumab can cause a modest but statistically significant increase in BMD after 12 months of treatment. This increase is smaller than that obtained in patients not previously treated, but larger than the increase obtained in patients who switch from oral bisphosphonate to Zoledronate IV. This improvement is also detectable in patients who had previously experienced a poor response in terms of BMD to oral bisphosphonates.

Bisphosphonates → Teriparatide: ✓
The substitution of bisphosphonates with Teriparatide can determine a positive response in terms of BMD and indexes of bone anabolism, even in patients who have had a long exposure to oral bisphosphonates or have failed to respond to these drugs. Several studies have shown a transient decrease of femoral BMD after 12 months of therapy with Teriparatide, both in patients previously not treated as in patients already treated with anti-absorptive medications. This decrease is transient and does not affect the long-term densitometric response to Teriparatide.

Denosumab → Teriparatide: ✘
In the event of therapeutic failure of Denosumab, the choice of Teriparatide, while recommended by the IOF (substitution of a powerful anti-absorptive with an anabolic treatment), may cause further reduction in BMD both in the spine and in the femur. The pathophysiology is unclear, but it could represent the further stimulus by Teriparatide on a bone whose osteoclastic precursors are already hyperactive following cessation of inhibition by Denosumab.

Denosumab → Bisphosphonates: ✓
The bisphosphonates are the only treatment currently available capable to prevent the rebound of skeletal turn-over which follows suspension of Denosumab. This rebound is associated with an increase in the risk of fracture (vertebral fractures in particular). The optimal duration of treatment with Bisphosphonates remains uncertain, but in patients whose risk of fracture remains elevated it could be used as an intermediate stage in the sequence Denosumab → Teriparatide discussed above.

Teriparatide → Bisphosphonate/Denosumab: ✓
The decline in BMD, which follows suspension of Teriparatide after 24 months of treatment, may be prevented by bisphosphonates and Denosumab. These medications may also increase BMD (Denosumab significantly more than oral bisphosphonates).

References

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