Enhancing Treatment Success in Osteoporosis: Optimising the Use of Teriparatide

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Interview Summary

Osteoporosis, a chronic metabolic bone disease affecting over 200 million people globally, is characterised by low bone mass and microarchitectural deterioration, leading to an increased risk of fractures. The prevalence and associated healthcare costs of osteoporosis are substantial, with an estimated 27.6 million individuals in the European Union (EU) living with the condition in 2010. Fractures, particularly vertebral and hip fractures, are linked to reduced health-related quality of life and increased mortality risk.

While several efficacious osteoporosis treatments are available, none are suitable for permanent use. Instead, clinicians employ a sequential therapy approach in which patients transition between treatments, based on their individual risk factors. Here, Enrique Casado, rheumatologist at Parc Taulí Hospital Universitari, Sabadell, Spain; and Lothar Seefried, orthopaedic surgeon at Julius-Maximilians-Universität, Würzburg, Germany, explain the importance of early identification of at-risk individuals and personalised management strategies. They look at the evolving understanding of the osteoanabolic teriparatide, and what the last two decades of data tell us about its risks and benefits. The growing evidence base, they say, has

influenced regulatory and clinical changes regarding the use of teriparatide. They emphasise the agent's safety profile, and talk about its potential to reduce fracture risk within a short timeframe; as well as its place in sequential therapy.

OSTEOPOROSIS OVERVIEW

Osteoporosis is the most common chronic metabolic bone disease globally. Characterised by low bone mass, deterioration of bone tissue, and disruption of the bone microarchitecture, it affects more than 200 million people.[1]

The bone remodelling cycle involves the removal of older bone and its replacement with new bone. Via this process, which involves the absorption of obsolete and/or physiologically useless bone and reconstruction of viable and mechanically competent bone, bone tissue is continuously restructured. If the resorption rate is higher than the formation rate, or the process is not well orchestrated, it leads to bone loss and reduced bone mass or compromised bone quality, predisposing people to an increased risk of fractures.[1]

Hereditary traits, age, and lifestyle factors all impact on the risk of osteoporosis and fractures. The most frequent risk factors include menopause, and the associated loss of bone-protective sex hormones; ageing and the natural 'slowing down' of bone remodelling; and the use of glucocorticoids, which initially increase bone loss as well as compromising bone formation in the long term.[1] Other common risk factors for osteoporosis and fracture include excessive alcohol consumption; smoking; and low calcium intake, either through diet or disease-related malabsorption (potentially due to inflammatory diseases such as rheumatoid arthritis).[1]

In the EU, an estimated 32 million people, or 5.6% of the total population, were living with osteoporosis in 2019. Of these, 25.5 million were females and 6.5 million were males, and together they experienced 4.3 million fragility fractures each year. Such fractures can be painful and cause functional disability, as well as reduced health-related quality of life and increased risk of mortality. Every year, nearly 250,000 people in Europe die as a direct consequence of hip or spine fractures.[2]

Casado said: "As a rheumatologist, I mainly see patients with vertebral fractures. They suffer from pain, from deformities of the spine, and some of them even can have pulmonary restrictions. However, hip fracture is the most dangerous fracture. These patients tend to be older and they can suffer severe complications or even can die in the first year following the fracture.[3] Those who, fortunately, survive can suffer from health-related quality of life impairment because they can't work or do the things they used to do, and may need a wheelchair or other assistance."

In addition, fractures are associated with high healthcare costs. A 2020 systematic review found the average direct annual cost of treating osteoporotic fractures in Canada, Europe, and the USA alone to be between 5,000–6,500 billion USD. This figure does not include indirect costs, such as those related to disability and loss of productivity.[4]

ACT EARLY. REDUCE FRACTURES.

With several osteoporosis therapies available, clinicians have the opportunity to identify and manage the condition, and help prevent fractures before they occur, noted Seefried. "We now have agents and regimens that significantly reduce fracture risk, and the prognosis is really good, much better than what it was in the past. There is no need for people to be scared or concerned because we can anticipate fracture risk and manage osteoporosis so that patients can live a normal and, at least with regard to osteoporosis, untroubled life." Identifying patients before they experience fractures "is the most challenging and

intriguing aspect" of osteoporosis care, he went on, adding that there is a "large degree of individuality" around the risk factors.

Casado and Seefried agreed that all people deemed to be at risk of developing or having osteoporosis should undergo bone mineral density (BMD) testing and individualised fracture risk assessment, which may include the use of established tools, such as the Fracture Risk Assessment Tool (FRAX), according to applicable guidelines.[5] The next step would be the creation of an individualised management strategy, tailored to the patient's age and risk of fracture.

The various types of available osteoporosis treatment include anabolic agents and antiresorptive drugs. Anabolic agents, such as teriparatide, abaloparatide, and romosozumab, increase bone formation over time by targeting osteoblasts, while antiresorptive drugs, including bisphosphonates, selective oestrogen receptor modulators, and denosumab, primarily reduce bone resorption.[5] Unlike in most chronic diseases, however, the use of approved treatments tends to be limited to a single drug at a fixed dose and frequency.[6] As such, international guidelines recommend sequential therapy, or initiating treatment with one class of drug before transitioning to another, to capitalise on their respective benefits.[5]

As the different agents have different modes of action, and some can impact on the efficacy of those that follow,[5] it is important to plan the sequence early, said Casado and Seefried. "The long-term perspective is critical," observed Seefried. "We have a lot of treatment options for osteoporosis, but none are suitable to continue for 25 years. We have to change the medication and the drug regimen over time, and that means establishing individualised sequences of treatment." His aim when treating patients with osteoporosis, he explained, was to keep the bone resilient and avoid supressed bone turnover, so that treatment could still be adjusted 10 or 15 years in the future.

RISK-BASED SEQUENTIAL THERAPY PLANNING

Current clinical guidelines recommend using individual fracture risk as the starting point for sequential therapy.[5] Following diagnosis of osteoporosis, clinicians can use various algorithms to approximate anticipated future fracture risk as much as possible. It has become common practice to not only define thresholds for treatment initiation, but to further differentiate between patients at high and very high fracture risk, the doctors explained.[5] Fracture risk assessment tools, such as FRAX, Qfracture, Garvan, and others, consider a variety of risk factors for fracture, like age and sex, BMD, prior fractures, smoking and alcohol use, as well as various secondary causes of osteoporosis.[1] People who have particularly critical risk factors, such as a recent (within 1–2 years) sentinel fracture, or a particularly low BMD and glucocorticoid intake, are considered to be at imminent risk of subsequent fracture.[7] Internationally, the majority of current guidelines recommend that patients at very high or imminent risk of fracture be initiated on an osteoanabolic agent, such as the fast-acting teriparatide, followed by an antiresorptive medication.[5]

"We have to look at the individual risk, which may be high, very high, or at the borderline of high to very high, to guide the individual treatment. Where there are indicators of elevated imminent risk, we have to start a treatment that is not just effective over time, but that also has rapid efficacy so as to preclude and to limit that immediate risk," said Seefried.

However, while risk is an important factor, it is not the sole consideration. As Casado explained: "We have to know the characteristics of the patients: not just their age but also their comorbidities." For example, bisphosphonates should be used selectively and with caution in people living with chronic kidney disease,[8] and needle phobia often precludes the use of subcutaneous treatments.

TERIPARATIDE

Teriparatide is a parathyroid hormone analogue. The osteoanabolic increases the formation of new bone tissue.[9] It initiates bone growth in days or weeks by stimulating osteoblast activity, decreasing osteocyte sclerostin expression, and inducing osteoblastogenesis. It also increases osteoblast receptor activator of nuclear factor κB ligand production, activating osteoclasts and resorbing bone.[10]

Casado said: "Teriparatide is very fast acting. It increases BMD and changes bone microarchitecture, increasing the cortical and trabecular thickness, offering benefit in a very short time."[11] Seefried agreed, calling it a "fast approach" to mitigating increased fracture risk at short notice. "Teriparatide offers the option of an enhanced remodelling process, which includes the reduction of deteriorated old bone, replacing it with newly structured bone, which is more sustainable, and that makes a good starting point for subsequent treatment options."[11]

The use of teriparatide has evolved since it was first approved by the U.S. Food and Drug Administration (FDA) in 2002,[12] and then the European Medical Agency (EMA) the following year.[13] These approvals were based on Phase III clinical trials that were originally designed to monitor 36 months of treatment, but which were halted early after preclinical studies found an increased risk of osteosarcoma in rats treated with high doses for almost their full lifespan. The trial data, which covered an average 19-month treatment course, however, showed efficacy and tolerability. The FDA approved teriparatide for the treatment of osteoporosis in patients at very high risk for fracture, with a black box warning regarding the potential risk of osteosarcoma, and a 2-year lifetime limitation of use. Manufacturers were also required to assess for risk of osteosarcoma in humans.[14]

Since then, the scientific community has amassed more than two decades of data that provide a much better understanding of the risks and benefits of teriparatide. For example, two large cohort studies that linked pharmacy claims data with data from cancer registries showed no increase in osteosarcoma among patients using teriparatide when compared with unexposed groups, or against the expected background incidence of the disease.[14] As such, in 2020 the FDA removed the black box warning for osteosarcoma.[4,15]

"After 20 years of teriparatide use, and a very accurate system of pharmacovigilance, there is no evidence of these risks. The risk of tumours, including osteosarcoma, in rats does not appear to be a concern in humans," said Casado. Seefried added that, while there was "no need to be concerned," this is an issue that often looms large in the minds of patients. "It's interesting because when you instruct patients about the treatment and they look it up themselves, osteosarcoma is always the first question they bring up," he said. It is important, then, for clinicians to mitigate these concerns, and explain that the vast majority of patients are "really doing well on the treatment" and "hardly feel any side effects," he said. Casado explained that some of his patients on teriparatide did experience minor side effects, such as headache or leg cramps.[16] In his experience, these effects tend to occur at the start of the treatment course, and normally decrease over time. "Some patients do decide to change treatment because of this, but not many," he said. The doctors also said that while some patients do develop hypercalciuria, it was relatively rare, and was not often clinically relevant.[16]

Turning to the increase in maximum treatment length, both doctors agreed that a full 24-month course of treatment was the most beneficial. Studies have shown 'highly significant' increases in BMD between 18–24 months of therapy,[17] and a 2015 review of the available evidence found that patient outcomes and skeletal health appeared to be improved by the full 24-month continuous course, as opposed to 18 months of treatment.[9] The review authors noted that the biochemical and histological data suggest ongoing bone formation throughout the 24 months, resulting in increases in bone mass and strength, and a decreased fracture risk. While the

review highlighted that no randomised controlled trial comparing the efficacy of 18- and 24-month treatment has yet been performed, "the available information suggests that the full 24-month treatment course is important to achieve the best clinical outcomes."[9] Casado said: "During the first months of treatment, patients can show a decrease in hip BMD, because teriparatide can lead to some degree of cortical porosity. However, after the first 12 months of treatment, this porosity is filled with new bone that will go on to become mineralised, reflected in BMD gains."[9]

TERIPARATIDE AND SEQUENCING THERAPIES

The literature has shown the best outcomes are achieved when teriparatide is used before antiresorptives.[5,17,18] As such, clinical practice guidelines recommend osteoanabolics as a first-line treatment in very high-risk patients.[5]

"Teriparatide is a perfect starting point to enhance the remodelling process initially, and rebuild and restructure the bone before continuing with antiresorptives," said Seefried. Casado added that, based on the science, the best approach would be teriparatide followed by antiresorptives. He said: "To treat with osteoanabolics, particularly teriparatide, only after antiresorptive treatment failure, i.e., when the patient has suffered one or two fractures in high- or very high-risk patients, is simply too late."

In routine practice, however, antiresorptives are more readily available due to their lower cost, while their oral administration means that some patients find them easier to use. Casado went on: "We cannot stay with the idea we can only use osteoanabolics as a first-line in very high-risk patients, or after antiresorptives when the patient experiences treatment failure or an increase in fracture risk." It is important to note, though, that starting therapy with antiresorptives does not preclude the use of teriparatide later on. Clinicians should be aware that pre-treatment with antiresorptives will merely 'blunt' teriparatide's effect on BMD, but not reduce its antifracture effect.[17,18]

"When we have to start a patient on an antiresorptive for whatever reason," said Seefried, "we should always keep in mind that sooner or later they will require an osteoanabolic, so we should always have an approach that facilitates switching." Using a short half-life bisphosphonate, for example, may limit the antiresorptive activity that inhibits teriparatide efficacy. This is one way to "pave the way for osteoanabolic treatment later on," he observed.[19]

Particular care needs to be taken when switching from denosumab, due to a decrease in BMD, and the risk of rebound vertebral fracture after treatment discontinuation.[20] "The longer patients are on denosumab, the more challenging it becomes to transition them to teriparatide," said Seefried.[21] "No one should be so self-confident as to claim that this was easy-going, and wouldn't require diligent follow-up. There will always be a certain risk, which brings us back to the importance of planning the sequence early."

TERIPARATIDE CONTRAINDICATIONS

Asked about teriparatide contraindications, Seefried said it was important to be mindful of the patient's individual history and characteristics. Clinicians should, for example, be cautious in recommending the agent to patients who have experienced malignant disease, and previous radiation therapy is a clearly specified contraindication. Despite there being no evidence that the osteosarcoma risk seen in preclinical trials applies to humans, "we should be smart enough not to expose these patients at increased risk to teriparatide," he said. Any laboratory findings suggesting another metabolic bone condition, such as hyperparathyroidism or Paget's bone disease, should be evaluated mindfully before considering or initiating teriparatide.[16]

Casado said that clinicians also need to look at other patient characteristics. Teriparatide

is administered as a subcutaneous daily injection and requires self-administration, so may not be suitable for people with needle phobia, or those with limited dexterity, for example.

Although older age is not a formal contraindication, teriparatide is often avoided for these patients in routine practice. Both doctors, however, said they would not withhold the treatment on the basis of age alone. "I'm very open to prescribing osteoanabolics, specifically teriparatide, to elderly patients, even if they are 85 or older. If they are self-sustained and want to keep their lifestyle, there's no reason to deny them teriparatide," said Seefried. These are very high-risk patients, with the highest risk of fracture, said Casado. "It means that the number needed to treat to reduce fragility fracture risk is lower than in any other group," he went on. "If they have a fracture risk that justifies teriparatide, of course it is smart to give them this 2-year treatment, improve their bone quality, make it sustainable, and then continue with antiresorptives for the rest of their lifetime."

BIOSIMILARS, HEALTH ECONOMICS, AND FUTURE DIRECTIONS

Casado and Seefried explained the decision to restrict the use of teriparatide as a first-line therapy for very high-risk patients had, at least in part, been influenced by its cost.

"The reasons for it being used so cautiously and conservatively may have to do with costs," said Seefried. "I consider this highly relevant, because the cost difference between teriparatide and the antiresorptives, as compared with the costs of inappropriate treatment and the fractures that can happen otherwise, is negligible." Casado agreed, adding that changing matrix architecture and increasing bone strength can avoid future fractures and the associated comorbidities. "This is good for patients, but it is also good for governments and administrations because, by avoiding fractures, we can also save money."

Both doctors said they used teriparatide early in the sequence, with Seefried adding that, "from a scientific perspective, everyone would think that this is appropriate." While guidelines are now moving in this direction, "they are not there yet," and though the FDA has lifted the once-per-lifetime limitation on teriparatide treatment, the European label remains more restrictive, said Seefried.

The emergence of biosimilars in recent years has widened access, the doctors went on. Biosimilars are biological medicines which are highly similar to their 'reference medicine', or a previously approved biological medicine. Due to the 'living' nature of such products, there may be minor natural variability between the biosimilar and the reference medicine, but regulators have strict controls in place to ensure there are no clinically meaningful differences.[22]

Biosimilars are approved according to the same standards of pharmaceutical quality, safety, and efficacy that apply to all biological medicines. Biosimilar manufacturers are obliged to demonstrate that their products have a high similarity, in terms of structure, biological activity and efficacy, safety, and immunogenicity profile, to the reference medicine.[22]

"Biosimilars have changed our clinical practice, and I think some guidelines have changed thanks to them. They have lowered the price, and expanded the pool of patients who can benefit from teriparatide," said Casado. Seefried described biosimilar teriparatide as a "tremendous step forward." "Sick funds, funding agencies, and insurance companies all around the globe have developed an open-minded approach to patients being treated with teriparatide since we have had biosimilars on the market, and that is being reflected in the common practice," he said.

The updated guidelines, allowing for the use of osteoanabolics in all very high-risk patients from diagnosis, "is a very beneficial development," he went on, concluding that "everyone should be made aware of this opportunity to improve patient care."

References

1. Sözen T et al. An overview and management of osteoporosis. Eur J Rheumatol. 2017;4(1):46-56.
2. International Osteoporosis Foundation (IOF). Scorecard for osteoporosis in Europe: Scope 2021 summary report. 2021. Available at: https://www.osteoporosis.foundation/sites/iofbonehealth/files/2022-01/SCOPE%20Summary%20Report.pdf. Last accessed: 9 April 2024.
3. Clynes MA et al. The epidemiology of osteoporosis. Br Med Bull. 2020;133(1):105-17.
4. Kemmak AR et al. Economic burden of osteoporosis in the world: a systematic review. Med J Islam Repub Iran. 2020;34:154.
5. Mondo I et al. Using sequential pharmacotherapy for the treatment of osteoporosis: an update of the literature. Expert Opin Pharmacother. 2023;24(18):2175-86.
6. Leder BZ et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. 2015;386(9999):1147-55.
7. Javaid MK et al. Assessment and management of imminent fracture risk in the setting of the fracture liaison service. Osteoporos Int. 2022;33(6):1185-9.
8. Toussaint ND et al. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. Clin J Am Soc Nephrol. 2009;4(1):221-33.
9. Lindsay R et al. Teriparatide for osteoporosis: importance of the full course. Osteoporos Int. 2016;27(8):2395-410.
10. Sauhta R et al. The sequential therapy in osteoporosis. Indian J Orthop. 2023;57(Suppl 1):150-62.
11. Guelman R et al. Effect of teriparatide on bone mineral density and bone markers in real-life: Argentine experience. Int J Endocrinol. 2023;DOI:10.1155/2023/9355672.
12. U.S. Food and Drug Administration (FDA). Drug approval package: forteo [teriparatide (rDNA origin)] injection. 2002. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-318_Forteo.cfm#:~:text=Approval. Last accessed: 25 March 2024.
13. European Medicines Agency (EMA). Forsteo. 2022. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/forsteo. Last accessed: 25 March 2024.
14. Krege JH et al. Teriparatide and osteosarcoma risk: history, science, elimination of boxed warning, and other label updates. JBMR Plus. 2022;6(9):e10665.
15. European Medicines Agency (EMA). Forsteo: procedural steps taken and scientific information after the authorisation. 2022. Available at: https://www.ema.europa.eu/en/documents/procedural-steps-after/forsteo-epar-procedural-steps-taken-and-scientific-information-after-authorisation_en.pdf. Last accessed: 25 March 2024.
16. European Medicines Agency (EMA). Movymia, INN-teriparatide. Annex I summary of product characteristics. 2021. Available at: https://www.ema.europa.eu/en/documents/product-information/movymia-epar-product-information_en.pdf. Last accessed: 25 March 2024.
17. Obermayer-Pietsch BM et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. J Bone Miner Res. 2008;23(10):1591-600.
18. Miller PD et al. Teriparatide: label changes and identifying patients for long-term use. Cleve Clin J Med. 2021;88(9):489-93.
19. Leder BZ. Optimizing sequential and combined anabolic and antiresorptive osteoporosis therapy. JBMR Plus. 2018;2(2):62-8.
20. Anastasilakis AD et al. Denosumab discontinuation and the rebound phenomenon: a narrative review. J Clin Med. 2021;10(1):152.
21. Tay WL, Tay D. Discontinuing denosumab: Can it be done safely? A review of the literature. Endocrinol Metab (Seoul). 2022;37(2):183-94.
22. European Medicines Agency (EMA). Biosimilars in the EU: information guide for healthcare professionals. 2023. Available at: https://www.ema.europa.eu/en/documents/leaflet/biosimilars-eu-information-guide-healthcare-professionals_en.pdf. Last accessed: 3 April 2024.