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Personalising osteoporosis treatment for patients at high risk of fracture

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Although a number of effective drugs are available for the treatment of osteoporosis,[1] the therapeutic strategy for fracture prevention has generally been rather simplistic—ie, a one-size-fits-all approach. Thus, most patients who meet criteria for pharmacological treatment[2] are offered bisphosphonates at standardised doses as first-line therapy. According to patient or physician preference, some patients might be offered alternatives, including denosumab, or if fracture risk is deemed particularly high, one of the bone formation-stimulating drugs (teriparatide, abaloparatide, or romosozumab) might be used.[1] However, to date, little effort has been made to systematically personalise the pharmacological approach for patients with osteoporosis on the basis of refined risk stratification.

The publication of clinical practice guidelines for the pharmacological management of osteoporosis by the Endocrine Society,[3] in which the authors proposed an algorithm based on gradations of fracture risk, represents an important step towards personalised treatment stratified by fracture risk. In the guidelines, four categories of risk are defined (table): low, moderate, high, and very high risk. Despite this thorough classification, the guidelines do not specify whether bisphosphonates, denosumab, teriparatide, abaloparatide, or romosozumab would be the preferred treatment for specific risk groups and also do not address combination therapy in patients—eg, in patients who are at very high risk of fracture.

In the context of combination therapy, the study by Joy Tsai and colleagues[4] in *The Lancet Diabetes & Endocrinology* is of particular interest. In their previous Denosumab and Teriparatide Administration (DATA) study,[5] the investigators showed that the combination of the bone formation-stimulating drug, teriparatide (used at the standard US Food and Drug Administration approved dose of 20 μg daily), with the potent anti-resorptive drug, denosumab, increased bone mineral density (BMD) to a greater extent than either drug alone. The DATA study was of particular importance because it was the first combination treatment found to unequivocally improve BMD outcomes compared with either drug alone, and thus it offered a new approach for the treatment of patients with osteoporosis at high risk of fracture. In the DATA-HD study,[4] the investigators combined a higher dose of teriparatide (40 μg daily) with denosumab and showed that this combination is substantially better at improving BMD at multiple sites than the standard dose combination (teriparatide 20 μg daily). At 15 months, mean spine aBMD had increased to a significantly greater extent in the

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40 μg group (17·5% [SD 6·0] increase) than the 20 μg group (9·5% [3·2]).[4] Mean aBMD at the femoral neck and total hip had also increased to a significantly greater extent in the 40 μg group (6·8% [4·1] increase at the neck, 6·1% [3·4] increase at the hip) than the 20 μg group (4·3% [3·7] increase at the neck and 3·9% [2·9] increase at the hip) at 15 months.[4] DATA-HD is important because the increases in BMD and estimated bone strength using high dose teriparatide and denosumab seem to be greater across multiple skeletal sites than any single drug regimen (including the recently approved sclerostin antibody, romosozumab), or any previous combination treatment. Additionally, the high dose teriparatide and denosumab combination was just as well tolerated as the conventional dose teriparatide and denosumab combination.

The results of DATA and DATA-HD indicate the possibility of refining treatment for patients with osteoporosis at high risk of fracture and personalising treatment for these patients beyond the one-size-fits-all approach currently used (ie, predominantly prescribing bisphosphonates). On the basis of the findings of DATA-HD,[4] a subset of patients at high risk of fracture and perhaps many patients who would be categorised as very high risk categories according to Endocrinology Society clinical guidelines (table)[3] could be considered for treatment with high dose teriparatide and denosumab to rapidly and substantially increase their BMD, which in many cases could perhaps result in the achievement of non-osteoporotic BMDs.

The authors note caveats to their approach, including the small size of the DATA-HD, which limits the direct assessment of fracture incidence. Although the authors advocate the need for a larger trial powered to investigate anti-fracture efficacy, the costs associated with such a trial make it unlikely, particularly since the patent for teriparatide will expire in 2019. Increasing evidence from meta-regression analyses of published clinical trials[6] suggests that change in BMD is a robust surrogate endpoint for fracture, and for patients at very high risk of fracture the benefits of the marked increases in BMD observed with combination therapy, such as those in DATA-HD, are likely to offset the uncertainty that BMD gains will translate into anti fracture efficacy. However, considering that the dose of teriparatide approved by the US Food and Drug Administration is 20 μg per day, physicians would either need to prescribe the standard dose in combination with denosumab (as given in DATA[5]) or prescribe the higher dose off-label, following appropriate discussions with the patient regarding risks and benefits. Thus, it is unlikely that high dose teriparatide and denosumab would be widely used, but in selected patients it could be an important option.

Cost remains an issue. Based on current pricing estimates,[7] the cost of the combination of teriparatide at 40 μg per day and denosumab used in DATA-HD[4] given for 15 months would be approximately US$76 000. As noted by the authors, this cost might decrease when teriparatide comes off patent in August 2019, although considering recent trends in generic drug pricing,[8] a price decrease is by no means certain. Moreover, the experience of most clinicians in the USA is that gaining insurance company approval for combination therapy for osteoporosis is virtually impossible, in marked contrast to other chronic diseases such as hypertension, diabetes, and hyperlipidaemia, in which a combination of drugs are often used on the basis of disease severity.

Clinicians also need to be aware of another important issue following combination (or anabolic) skeletal therapies: in the absence of continuing anti-resorptive therapy (eg, a bisphosphonate or denosumab), the increases in BMD are lost over time.[3] Thus, it is crucial that if anabolic or combination therapy is used, this should be followed by sustained anti-resorptive therapy.[3] Continuing denosumab in patients at very high risk of fracture might be the most efficacious approach, since the optimal protocol for switching from denosumab to a bisphosphonate remains to be established. Specifically, a bisphosphonate might not be effective following denosumab treatment because the bisphosphonate might not be appropriately incorporated into remodelling sites when remodelling is markedly reduced by denosumab.

Despite the limitations of DATA[5] and DATA-HD,[4] these trials have established the efficacy of combination therapy at least on BMD, which is a viable surrogate for fracture risk.[6] Furthermore, high dose teriparatide plus denosumab seems to have superior efficacy to other available options. Ideally, large-scale fracture trials should be done to compare combination therapy with monotherapy, but for many high-risk patients, the BMD findings might be sufficient to warrant a course of combination therapy with high dose teriparatide and denosumab to markedly improve their osteoporosis.

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Table:

Fracture risk categories, defined by the Endocrine Society clinical practice guidelines for pharmacological management of osteoporosis[3]

	Definition
Low risk	No prior hip or spine fractures, BMDT-score at the hip and spine both above −1 0, and 10-year hip fracture risk <3% and 10-year risk of major osteoporotic fractures <20%
Moderate risk	No prior hip or spine fractures, BMDT-score at the hip and spine both above−2 5, or 10-year hip fracture risk <3%or risk of major osteoporotic fractures <20%
High risk	Prior spine or hip fracture, or a BMDT-score at the hip or spine of−2 5 or below, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk≥20%
Very high risk	Multiple spine fractures and a BMDT-score at the hip or spine of−2 5 or below

BMD=bone mineral density.