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Doctopic: Analysis and Interpretation THELANCETDE-D-19-00736 19TLDE0736 PII: S2213-8587(19)30348-1

**Odanacatib: the best osteoporosis treatment we never had?**

Current drugs used to treat osteoporosis target bone turnover. Oestrogens and oestrogen-receptor modulators in post-menopausal women, and bisphosphonates and denosumab in both sexes, all decrease bone resorption, and anabolic drugs such as teriparatide increase bone formation. However, the outcome of treatment with these drugs is affected by coupling of bone turnover; ie, decreased resorption also results in less bone formation and increased formation is associated with increased resorption. Odanacatib, a selective cathepsin-K inhibitor, can uncouple bone turnover so that bone resorption is reduced without substantially inhibiting bone formation. Additionally, a phase 2 study showed that odanacatib improved bone mineral density with no plateau in effect.1 In the *Lancet Diabetes & Endocrinology*, Michael McClung and colleagues2 present the results of their randomised placebo-controlled trial (LOFT) and extension study (LOFT Extension).

The trial was large enough to show an effect on the primary outcome of vertebral fracture and clinical hip and non-vertebral fracture. Combined incidences from LOFT plus LOFT Extension for odanacatib versus placebo were: radiographic vertebral fractures 4·9% (341/6909) versus 9·6% (675/7011), HR 0·48, 95% CI 0·42–0·55; hip fractures 1·1% (86/8043) versus 2·0% (162/8028), 0·52, 0·40–0·67; and non-vertebral fractures 6·4% (512/8043) versus 8·4% (675/8028], 0·74, 0·66–0·83; all p<0·001. These results compare favourably with those of other antiresorptive drug trials.3,4

So why is this novel drug, which was associated with a sustained increase in bone mineral density and reduction in fracture risk, not available to clinicians or patients? There was an increased risk of several adverse events including morphoea-like skin reactions, femoral shaft fractures (including possible atypical femur fractures), and major adverse cardiovascular events (stroke, new-onset atrial fibrillation, and atrial flutter) in those receiving odanacatib in the original trial. In the extension study, treatment with odanacatib continued to reduce risk of fracture, but evidence of adverse events also continued. Although the results of the extension study were masked, only half of the participants from the original study were included, and those from Asian and Pacific study centres were under-represented, which might have changed the adverse event risk profiles.

Morphoea-like skin reactions occurring with odanacatib and other cathepsin-K inhibitors have been hypothesised to be due to inhibition of cathepsins B, L, and S, expressed by skin fibroblasts, or interference with the effect of cathepsin-K on homeostasis of the dermal extracellular matrix.5 The increased incidence of femoral fracture with odanacatib was disappointing, as it had been hoped that suppression of bone resorption, thought to be a cause of atypical femur fractures, would be ameliorated by maintenance of bone formation with the drug. On a positive note, no cases of osteonecrosis of the jaw, another adverse effect associated with antiresorptive drugs, occurred; although this result might reflect the rarity of this event, for which evidence of risk has mostly been derived from observational studies.3

The increased risk of major adverse cardiovascular events with odanacatib in the LOFT plus LOFT Extension study included an increased absolute risk of stroke (187 [2·3%] in the odanacatib group vs 137 [1·7%] in the placebo group; HR 1·37, 95% CI 1·10–1·71; p=0·0051), equivalent to an absolute risk increase (number needed to harm) of approximately 0·15% (660) per year. There was also a numerically greater incidence of new-onset atrial fibrillation and atrial flutter (odanacatib *vs* placebo HR 1·17, 95% CI 0·93–1·46, (164 [2·0%] *vs* 141 [1·8%]; p=0·18), which might have contributed to the increased stroke risk. However, these cardiovascular risks should be viewed in the context of other drug treatments for osteoporosis, some of which have also shown potential cardiovascular risks. Although bisphosphonates have no overall effect on major adverse cardiovascular events, treatment with zoledronic acid has been linked to an increased risk of atrial fibrillation.2 Additionally, after strontium ranelate was briefly withdrawn from the UK market in August 2017, it returned to the market in January 2019 to the UK with prescribing restrictions relating to cardiovascular risks, venous thromboembolism, and skin reactions.7 Overall, the risk profile of odanacatib might be no worse than some alternative treatments that are currently licensed. However, Merck, the manufacturer of odanacatib, decided in 2016 not to seek regulatory approval for its use, stating “the increased risk of stroke in our phase 3 trial does not support further development”.8

So, is odanacatib the best treatment for osteoporosis that we never had, or will it be similar to (at least for some) the anti-sclerostin monoclonal antibody romosozumab?9 Romosozumab is another highly effective drug that increases bone mineral density and reduces the risk of fracture when given sequentially with antiresorptive drugs, but was initially refused marketing authorisation in Europe because of a risk of major adverse cardiovascular events compared with alendronic acid. However, it has received a positive opinion from the European regulatory authorities, although it appears likely that treatment will be restricted to postmenopausal female patients at high risk of fracture.10 Given that inexpensive efficacious treatments are already available, we could make better use of such drugs by targeted case finding and treatment in primary care. Patient adherence to oral bisphosphonate therapy can be poor but could be improved, while treatment with parenteral drugs such as zoledronic acid and denosumab might be best targeted at those with the highest risk of fracture. The costs of some treatments, including teriparatide, currently limit their use but the availability of biosimilars might change this landscape in the future and access to all treatments could be improved. Diagnostic accuracy, including access to bone mineral density scanning, and variations in provider compliance, including secondary prevention through fracture liaison services, are also areas where improvements in clinical care could be made. There is plenty to work on, while we await the magic bullet.

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