Why use parenteral therapies for osteoporosis?

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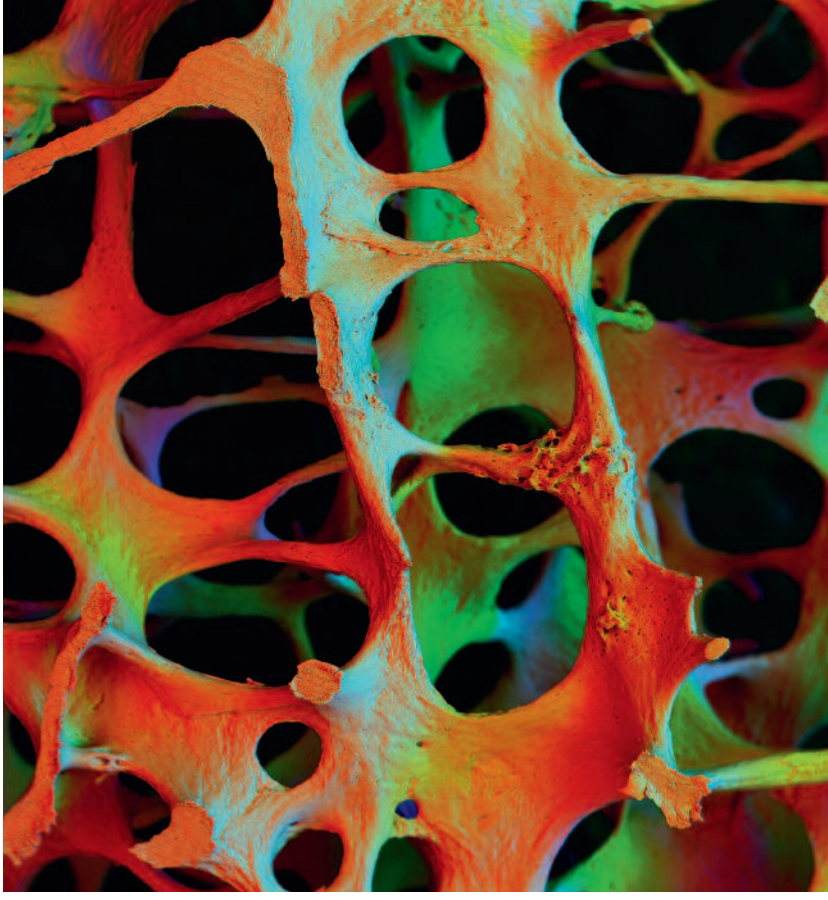
Treatment options for osteoporosis have dramatically changed over the past 15 years. The newer parenteral therapies, zoledronic acid, denosumab and teriparatide, are all effective treatment options with differing mechanisms of action. Here we review these new agents and compare their relative merits with existing oral medications for osteoporosis.



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Commentary from the Editor-in-Chief

This lucid article focuses on a specific topic in osteoporosis pharmacotherapy. The reader is reminded that in people diagnosed with osteoporosis, excluding secondary causes of osteoporosis, optimising both calcium and vitamin D status and also falls prevention strategies, are also important in any management approach to osteoporosis.

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Key points

- **Treatment of osteoporosis reduces mortality, as well as preventing further fractures, yet fewer than 20% of people in Australia with a previous osteoporotic fracture are actually treated for osteoporosis.**
- **Treatment options for osteoporosis now include bone-building (anabolic) and antiresorptive drugs, a choice of oral or parenteral administration, and varying dosing regimens from daily through to yearly administration.**
- **Longer dosing intervals for zoledronic acid and denosumab largely eliminate the issue of self-determined adherence and persistence.**
- **A parenteral route of administration for treatment of osteoporosis does not automatically confer better efficacy.**

Osteoporosis is a common problem in Australia, with two in five women and one in eight men aged 70 years and over having osteoporosis according to bone mineral density (BMD) criteria.[1] The incidence of low trauma fracture is even higher.[2] Although morbidity and mortality are highest following a hip fracture there is an increased risk of mortality following any low trauma fracture.[2-4] Treatment of osteoporosis reduces mortality, as well as preventing further fractures,[5-7] yet fewer than 20% of people in Australia with a previous osteoporotic fracture are actually treated for osteoporosis.[8-10]

Treatment options for osteoporosis have dramatically changed over the past 15 years. Options now include bone-building (anabolic) and antiresorptive medications, choice of oral or parenteral administration, and varying dosing regimens from daily through to yearly administration (see Table 1). Three new parenteral antiosteoporotic therapies are available in Australia – zoledronic acid, denosumab and teriparatide. This article discusses their mechanism of action, efficacy, side effect profile, and how they fit into the current osteoporosis treatment schema.

Zoledronic acid

Zoledronic acid is a potent intravenous bisphosphonate agent. It is administered by intravenous infusion over 15 minutes at a dose of 5 mg once per year. It is currently subsidised on the PBS (see Table 2 for details) for up to six years of treatment.

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Table 1. Mechanism, delivery method, dose frequency and duration of available drugs for osteoporosis

Medications	Mechanism		Delivery method			Dose frequency	Current prescribing duration
	Antiresorptive	Anabolic	Oral	Subcutaneous	Intravenous		
Alendronate	+		+			Daily or weekly	Unlimited †
Risedronate	+		+			Daily, weekly or monthly	Unlimited †
Zoledronic acid	+				+	Yearly	6 years
Raloxifene	+		+			Daily	Unlimited
Strontium ranelate*	+	(+)	+			Daily	Unlimited
Teriparatide		+		+		Daily	18 months
Denosumab	+			+		Six-monthly	3 years

* Strontium ranelate may have other effective mechanisms of action also.
† Review ongoing prescribing after 3 to 5 years particularly for longer-acting bisphosphonates, although note it may be appropriate to continue treatment in many patients.

Mechanism of action

As with all aminobisphosphonates, zoledronic acid targets bone surfaces throughout the skeleton, where it is then internalised by osteoclasts and inhibits their function and survival.[11]

Evidence of efficacy

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) pivotal study was a randomised, placebo-controlled trial in nearly 8000 women with osteoporosis. This study showed that a once-yearly infusion of 5 mg for three years reduced the risk of vertebral fracture by 70% (10.9% vs 3.3%) and hip fracture by 41% (2.5% vs 1.4%).[12]

Duration of therapy and frequency of dosing

Zoledronic acid has an extremely long duration of action, which raises questions about duration of therapy and frequency of dosing.

A three-year extension of the HORIZON trial, comparing patients continued on annual treatment with those switched to placebo, showed only a slight decrease in BMD at the femoral neck in the placebo group compared with the treatment group (with an absolute difference of 1%), with similar results at other sites. There was no significant difference in clinically evident vertebral and non-vertebral fractures between the two groups; however, there was a significantly higher rate of morphological vertebral fracture in patients who discontinued treatment (6.2% vs 3%).[13] A similar picture was seen for alendronate, another long-acting bisphosphonate.

The US Food and Drugs Administration recently recommended that patients on long-acting bisphosphonates (e.g. zoledronic acid and alendronate) be re-evaluated after three to five years regarding benefits of continuing bisphosphonate therapy, although they also indicated that patients with severe osteoporosis may still benefit from continued treatment.[14] It is worth noting that re-evaluation does not necessarily equate to automatic cessation of therapy and it may be entirely appropriate for many patients to continue treatment beyond this time frame.

Zoledronic acid has a prolonged effect in suppressing bone turnover, with antiresorptive effects seen out to five years after a single dose.[15] Whether a single dose confers the same fracture protection as repeated annual dosing is yet to be determined.

Side effects

Common adverse effects of zoledronic acid are flu-like post-dose symptoms (e.g. chills, fever, myalgia, nausea, bone pain), especially after the first infusion. These symptoms can be very debilitating but usually respond well to simple analgesics (e.g. paracetamol).[16] The initial HORIZON trial also found an increase in atrial fibrillation in the treatment group, although this was not found in other pivotal trials.[7,13] As it is renally excreted, zoledronic acid is contraindicated in patients with a creatinine clearance of less than 35 mL/min.

Use of bisphosphonates in patients with severe vitamin D deficiency has been associated with hypocalcaemia and, rarely, tetany. It is important, therefore, to ensure that vitamin D levels are adequate before zoledronic acid is administered (with 25-hydroxyvitamin D levels of at least 50 nmol/L, although arguably patients with osteoporosis may need a higher level for optimal bone health) and to consider patients' calcium intake. In the pivotal trials of zoledronic acid, all patients were given calcium and vitamin D therapy.[7,12]

Zoledronic acid is also used in patients with malignancy to prevent skeletal events, at considerably higher dosing frequency than that used for osteoporosis. In such patients, who often have several other comorbidities, including exposure to radiation and high-dose corticosteroids, zoledronic acid has been associated with osteonecrosis of the jaw (ONJ). In the pivotal trials of zoledronic acid for osteoporosis, there was no difference in ONJ between cases and controls.[7,12,13] A task force for the American Society for Bone and Mineral Research suggested the risk of ONJ for intravenous bisphosphonates at doses used in patients with osteoporosis is likely to be similar to that seen for oral bisphosphonates, estimated at one in 10,000 to 100,000 patient-treatment years;[17] although it was acknowledged that intravenous bisphosphonates had not been available for a long period of time.

Atypical fracture has been reported with zoledronic acid although it remains a very uncommon event (accounting for only six of the 310 cases reported in the literature by 2010).[18] With increasing use in the osteoporotic population this rate may increase.

Denosumab

Denosumab is the first available biological treatment for osteoporosis. It is a fully humanised monoclonal antibody against receptor activator of nuclear factor kappa-B ligand (RANK-L). It is administered at a dose of 60 mg subcutaneously at six-month intervals. It is subsidised on the PBS for three years of treatment (see Table 2).

Mechanism of action

RANK-L is secreted by osteoblasts and binds to its receptor (RANK) on osteoclasts, resulting in osteoclast recruitment, differentiation and activation. Blockade of RANK-L by denosumab potently decreases osteoclast activity; therefore, denosumab is a powerful antiresorptive drug. Denosumab is cleared by the reticuloendothelial system. There is a clear offset of action at about six months due to clearance of the drug.[19]

Evidence of efficacy

The Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial was a randomised placebo-controlled trial in nearly 8000 women with osteoporosis. Twice-yearly subcutaneous denosumab at a dose of 60 mg for three years reduced the risk of vertebral fracture by 68% (7.2% vs 2.3%) and nonvertebral fractures by 20% (8.0% vs 6.5%).[20]

Duration of therapy

Denosumab is different to long-acting bisphosphonates due to its near-complete cessation of action after about six months. Although long-acting in the sense of providing six months' antiresorption with a single dose, denosumab does not have a long persistence of bone protection effects. A strong offset rebound effect is seen when denosumab is ceased, with BMD falling back to the pretreatment baseline level within 12 months after discontinuation.[21] This suggests that once started, treatment needs to be continued or followed up by another antiosteoporosis medication.[22]

Side effects

In the FREEDOM trial, patients receiving denosumab had a significantly higher rate of cellulitis (0.3% vs 0.1%) and other skin disorders, including eczema, rash and pruritis (12% vs 9.1%) compared with placebo.[20] However, there was no difference in rates of cellulitis or eczema in the FREEDOM extension study.[23]

As is the case with bisphosphonates, use of this antiresorptive agent has been associated with hypocalcaemia with its risk of tetany, particularly in patients with vitamin D deficiency. Patients in the pivotal FREEDOM trial were supplemented with calcium and vitamin D according to their baseline vitamin D level. The authors adopt a similar approach in ensuring sufficient vitamin D and calcium as for zoledronic acid.

No cases of ONJ were observed in the pivotal FREEDOM trial. In the FREEDOM extension study, two patients previously on placebo were adjudicated as having ONJ within a few months of switching to denosumab; both cases subsequently healed.[23] When used at high dose in patients with malignancy to prevent skeletal events, the incidence of ONJ with denosumab is similar to that seen with zoledronic acid (2% vs 1.4% with zoledronic acid).[24]

One case of atypical fracture has now been reported in a patient treated with denosumab.

Denosumab is not renally excreted and therefore there is no dosage adjustment for patients with renal impairment.

Teriparatide

Teriparatide is a recombinant truncated form of parathyroid hormone (PTH), consisting of the first 34 amino acids of the hormone. It is administered subcutaneously at a dose of 20 μg once daily, and is PBS subsidised for men and women with severe osteoporosis (BMD T-score of -3 or less with a further osteoporotic fracture after at least 12 months of antiresorptive treatment following an initial low trauma fracture) for 18 months' treatment (Table 2).

Table 2. PBS indications for parenteral therapies for osteoporosis

Medication	Primary prevention	Secondary prevention
Zoledronic acid	Osteoporosis in a patient aged ≥70 years with a BMD T-score of -3.0 or less Corticosteroid-induced osteoporosis in a patient currently on long-term (>3 months), high-dose (at least 7.5 mg prednisolone or equivalent) corticosteroid therapy with a BMD T-score of -1.5 or less	Established osteoporosis in a patient with fracture due to minimal trauma
Denosumab	Osteoporosis in a woman aged ≥70 years with a BMD T-score of -2.5 or less	Established osteoporosis in a postmenopausal woman with fracture due to minimal trauma
Teriparatide		Severe, established osteoporosis in a patient with a very high risk of fracture who has a BMD T-score of -3.0 or less, has had two or more fractures due to minimal trauma, and has experienced at least one symptomatic new fracture after at least 12 months continuous therapy with an antiresorptive agent at adequate doses

Teriparatide is currently limited to specialist initiation but can be continued by a GP.

Mechanism of action

Teriparatide was the first available anabolic agent for osteoporosis. Although continuous exposure to excess PTH levels (as seen with primary hyperparathyroidism) causes bone resorption and osteoporosis, intermittent exposure to PTH has an overall 'bone-building' effect through its anabolic effects on osteoblasts via multiple mechanisms.[25]

Evidence of efficacy

Daily subcutaneous teriparatide at a dose of 20 μg compared with placebo in 1637 postmenopausal women with previous vertebral fracture resulted in a reduction in new vertebral fractures by 65% (14% vs 5%) and nonvertebral fractures by 53% (6% vs 3%). Although fewer hip fractures were seen in the treatment group compared with placebo, the numbers were extremely small and nonsignificant.[26]

Duration of therapy

After 18 months of treatment, patients should be commenced on an antiresorptive drug to protect against rapid loss of the bone gained.

Side effects

Serum calcium levels increase after each dose of teriparatide, but usually remain within the normal range (mean increase of 0.2 mmol/L) and in most patients return to normal before the next dose. Similarly, hypercalciuria can occur (median increase in daily excretion of 0.75 mg).[26] Teriparatide is therefore not advised for patients with primary hyperparathyroidism and/or a history of renal nephrolithiasis. Many physicians monitor serum calcium levels at one month and six monthly thereafter; calcium intake can be adjusted if significant hypercalcaemia occurs.[27]

In toxicology studies, prolonged exposure to high-dose teriparatide resulted in increased rates of osteosarcoma in rats.[28] Teriparatide should not be prescribed for patients at high underlying risk of osteosarcoma (e.g. due to previous bone irradiation, Paget's disease, open epiphyses); and use of PTH in younger patients with a long life expectancy should be carefully considered. However, no increase in risk of osteosarcoma has been observed in postmarketing surveillance to date.

So why use a parenteral medication?

Adherence to therapy

The mainstay of osteoporosis treatment for many years was oral bisphosphonate therapy, with the recent addition of strontium ranelate. Although these medications decrease osteoporotic fractures, in real-world use their efficacy is compromised by poor adherence and persistence, which is due to side effects, complex dosing instructions, and the often asymptomatic nature of osteoporosis.[29,30] A recent study found that only about 30% of patients persisted with their oral osteoporosis treatment for one year; even weekly and monthly dosing regimens had persistence rates of less than 50% at six months.[29]

The much longer dosing intervals for zoledronic acid and denosumab largely eliminate the issue of self-determined adherence and persistence. Although the daily injections required with teriparatide might be expected to reduce adherence and persistence, the severity of osteoporosis in patients who qualify for this treatment results in a highly motivated patient group.[31]

Side effect profile

Not surprisingly, gastrointestinal side effects (such as reflux or dyspepsia with bisphosphonates and diarrhoea with strontium) are usually eliminated with parenteral therapies.

Bioavailability

Many of the oral agents for osteoporosis have poor absorption, reduced further if patients do not take their medications exactly as recommended, resulting in low bioavailability. Parental administration bypasses these issues, ensuring optimal bioavailability.

Accessibility

Zoledronic acid and denosumab are listed on the PBS for both primary and secondary prevention of osteoporosis. Teriparatide is not a first-line treatment for osteoporosis and is available on the PBS only to patients fulfilling strict criteria (see Table 2).

Subcutaneous injections, as required for denosumab and teriparatide, can easily be given in the community. Intravenous delivery of zoledronic acid may be problematic for some general practices, although the pharmaceutical company supports a community infusion program including home administration.

Is efficacy improved?

It is important to note that a parenteral route of administration does not automatically confer better efficacy. Head-to-head comparisons between osteoporosis treatments are rare. A recent meta-analysis comparing the efficacy of the available treatments concluded that teriparatide was the most effective at preventing vertebral, hip and nonvertebral fractures, with bisphosphonates (oral and parenteral) and denosumab essentially tied for second place. Overall, however, the differences in efficacy of all drugs used in osteoporosis were small.[32]

Conclusion

It is exciting to see major breakthroughs in our understanding of bone biology resulting in new and effective treatments for osteoporosis. So to answer the question – why use parenteral therapies? – these newer medications allow better individualisation of our treatment options to meet the needs of patients with osteoporosis. **ET**

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A list of references is available on request to the editorial office.

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