Medication selection and patient compliance in the clinical management of osteoporosis

Charles A Inderjeeth, Andrisha-Jade Inderjeeth, Warren David Raymond

Background

Osteoporosis contributes significantly to morbidity and mortality. Antiresorptive therapy is effective in primary and secondary fracture prevention, but compliance with bisphosphonate therapy is poor, resulting in poorer patient outcomes.

Objectives

The objectives of this article are to aid clinicians’ treatment selection and improve patient adherence.

Discussion

A literature review of treatment options and factors contributing to poor patient treatment adherence was conducted for this article. The effectiveness of osteoporosis treatment is reduced because of poor adherence. This is associated with a lack of patient understanding of their condition, perception of fracture risk and concerns about adverse events. Appropriate treatment selection and novel oral and parenteral options may help improve compliance. Increasing treatment adherence requires clinicians to improve patient education. Discussion around patient preferences, implications of fragility fractures, minimising side effects and efficacy of treatment is essential despite the lack of any tangible ‘symptom’ benefit.

Fragility fractures are a common cause of hospitalisation, with significant cost, morbidity and mortality.1–3 Studies have demonstrated the benefit of treatment in primary prevention (first fracture) and treatment (prevalent fracture) in patients with osteoporosis.4–6

The association between poor adherence and fracture risk highlights the importance of compliance and persistence.7 Medications (alendronate, risedronate, zoledronic acid and denosumab) are listed on the Pharmaceutical Benefits Scheme (PBS)8 for primary and secondary fracture prevention in patients with prevalent fracture (Table 1).

Less than 20% of women and 10% of men with osteoporotic fractures receive treatment. Half do not take their treatment as prescribed (poor compliance) and 47% discontinue therapy within six months (lack of persistence).5,9 There are multiple reasons for poor adherence (eg patient perception, side effects, dosing intervals).4,7,9 This article considers the barriers to osteoporosis treatment, and discusses evidence-based strategies to improve adherence.

This informal literature review is an extension of the review completed by Lee et al in 2011.9 A MEDLINE search for more recent articles identified 50 additional articles from 2011 to 2015. The main search terms were ‘bisphosphonates’, ‘denosumab’, ‘osteoporosis’ ‘fracture’, ‘adherence’, ‘compliance’, ‘persistence’ and ‘efficacy’.

Patient perceptions and adherence

Forgetfulness is a concern that can be addressed using reminder systems.10–13

Table 1. Bisphosphonates available in Australia and approved indications for use8

<table>
<thead>
<tr>
<th></th>
<th>Osteoporosis</th>
<th>Corticosteroid-induced osteoporosis</th>
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<tr>
<td></td>
<td>Prevention</td>
<td>Treatment</td>
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<tr>
<td>Alendronate sodium</td>
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<tr>
<td>Risedronate sodium</td>
<td>✔</td>
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<tr>
<td>Risedronate sodium (enteric coated)</td>
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<td>Zoledronic acid</td>
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Electronic reminder systems are effective in improving patient drug compliance.11,12 While “forgetting” is a compliance issue, it is no longer recognised as a primary reason for poor compliance.13 Research suggests that some patients choose not to take medication.13 The major reasons for non-adherence include asymptomatic disease manifestation (“silent disease”) and an underestimation of the risk of fracture.14 The Global Longitudinal Study of Osteoporosis in Women found that only half of women with osteoporosis with multiple risk factors and receiving treatment for the disorder perceived themselves to be at increased risk of fracture.15

A Cochrane review on strategies to improve adherence highlighted the importance of more frequent patient interaction and regularly discussing compliance.16 Other studies cited the benefit of improving patient–provider relationships and patient education through regular follow-up, risk assessment and treatment monitoring.17,18

### Poor compliance compounds poor bioavailability of bisphosphonates

Oral bisphosphonates are poorly absorbed by the gastrointestinal system because of their low lipophilicity, large molecular structure and negative charge.19 Typically, only 0.3–1.0% of the dose is absorbed after ingestion.19,20 Taking these medications with food can decrease the bioavailability of the bisphosphonate by 60–90% because of physicochemical interactions between medicines and compounds present in the food, especially calcium and dairy products.20 Low bioavailability of oral bisphosphonates results in a clinically insignificant amount of the drug reaching its target, thereby diminishing efficacy.25 In some circumstances, measuring bone turnover markers may be useful in confirming compliance.

Fasting and the ‘30 minutes before food or drink’ requirement to improve bioavailability are commonly reported as reasons for patients failing to comply with oral bisphosphonate therapy.9,14 This barrier may be overcome by patients using enteric-coated, delayed-release weekly risedronate tablets, zoledronic acid infusion or subcutaneous denosumab.21 These may also be the preferred treatment modality for patients who, for example, are unable to fast for medical or other reasons, have cognitive impairment, or are identified by their clinicians as being poorly compliant patients.20 However, oral bisphosphonates should not be taken with calcium and dairy products.

### Adopting a patient-centred, flexible approach to dosing intervals

Bisphosphonate dosing intervals are noted as being inconvenient and a barrier to adherence.9,22,23 An alternative to frequent oral bisphosphonate dosing is an annual intravenous bisphosphonate (zoledronic acid) or six-monthly subcutaneous injections with denosumab, a rank ligand inhibitor. Patients have reported increased satisfaction with zoledronic acid or denosumab, compared with weekly oral bisphosphonate medications.9

Less frequent dosing (ie twice yearly denosumab or yearly zoledronic acid) may guarantee absolute compliance. However, because of needle phobia, acute phase reactions, infusion centre costs and scheduling reminders for both agents, persistence with zoledronic acid is not guaranteed. By contrast, more frequent dosing develops regular routines, which may aid adherence.9 Clinicians should optimise the dosing regimen on the basis of the patient’s preference and characteristics.

### Timing of initiation and clinician’s choice of treatments

Earlier treatment is recommended for patients presenting with fracture, as early fracture risk is greatest and benefits occur as early as three to six months.24 Results from randomised controlled trials investigating fracture prevention outcomes have confirmed differences in efficacy onset and offset between bisphosphonate options and treatment (Table 2).24

Inherent differences in dose, frequency and biological activity (binding affinity and potency) each affect time to efficacy onset and offset. A clinician’s choice of bone-sparing agent will aim to maximise benefit for treating the patient’s disease by balancing the time to efficacy onset with possible side effects while managing the patient’s risk of osteoporotic fracture(s). For example, for older and more frail patients at higher fracture risk and with a shorter life expectancy, the primary treatment goal would be the simplest dosing and fastest efficacy onset, as opposed to treatment durability (Table 3).24 Clinicians need to balance the benefit of a weekly routine versus the convenience

<table>
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<tr>
<th>Table 2. Results of all relevant studies showing the range of earliest onset of fracture efficacy and ranking of effect offset24</th>
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<tr>
<td><strong>Vertebral fracture</strong></td>
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<td>-----------------------</td>
</tr>
<tr>
<td>Aledronate</td>
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<td>Risedronate</td>
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<td>Zoledronic acid</td>
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Managing adverse upper gastrointestinal side effects with oral bisphosphonates – Balancing benefit and risks

Patients initiated on oral bisphosphonates are three times more likely to see their general practitioner (GP) within six weeks because of adverse upper gastrointestinal effects.25 Where this is not remediable, alternative modalities of bisphosphonate delivery, such as parenteral zoledronic acid, less frequent oral dosing or non-bisphosphonate options (denosumab or raloxifene), may be preferable.9

In circumstances where oral bisphosphonates remain the preference despite persistent gastrointestinal symptoms (rarely), co-administration with a proton pump inhibitor (PPI) or H2 receptor antagonists (H2RAs) may be considered. This co-administration is effective in reducing adverse gastrointestinal effects.23-25 Although some studies suggest that PPI use may be associated with a modest decrease in alendronate efficacy, a post-hoc analysis of three clinical trials with risedronate suggested no such effect.26-28 A reasonable approach to PPI prescription would be to use the lowest effective dose for the shortest duration, or consider prescribing an H2RA that has not been reported to affect bisphosphonate efficacy.23,24

Osteonecrosis of the jaw and atypical femur fractures with oral bisphosphonates – Balancing benefits and risks

Bisphosphonate prescription in Australia is declining, in part because of reports linking bisphosphonate use with osteonecrosis of the jaw.29-31 In Canada, over a three-year period, the cumulative incidence for bisphosphonate-associated osteonecrosis of the jaw was 1.04 per 100,000 patient years in osteoporosis or metabolic bone disease, and 442 per 100,000 patient years in cancer patient observations.31 The risk is low with good dental hygiene and care, and precautions with timing of invasive dental care (wait three to six months after last dose where possible).31

Atypical fractures are reported to increase after three to four years of bisphosphonate therapy.23,24 Putting the risk into perspective, major osteoporotic fracture in women at high risk is 3100 per 100,000 patient years, and bisphosphonates reduce fractures by 20–70%; atypical fracture attributed to long-term bisphosphonate therapy is 78 per 100,000 patient years at eight years, and significantly many more osteoporotic fractures would be prevented.30,32-34

While the unlikely possibility of atypical fractures should be considered among patients who report unexplained thigh pain in the context of long-term bisphosphonate therapy, concern about over-suppression of bone turnover is not a reason to stop therapy in the majority of women at high risk for osteoporotic fracture.33

Consider the consequences of ceasing bisphosphonate treatment

Bisphosphonates accumulate in the bone and are variably released for years after treatment cessation. Hence, it is important to consider the clinical question of “how long to treat?” Answering this question requires holistic consideration of the patient’s risk factors, therapeutic options and differences in onset and offset, which are drug-specific.

Data from long-term studies with bisphosphonates (up to 10 years) suggest that some patients may be able to take a break from treatment without incurring additional fracture risk after three to five years.29 The safety of ceasing denosumab is unknown at this stage because of concerns about rebound increase in bone turnover and risk of fracture. However, the continuing benefit of antiresorptive agents for up to 10 years in selected patients at high risk of fractures has been reported.28 The duration of initial treatment and length of any proposed treatment break should be guided by the patient’s absolute risk.29 Risk assessment tools (eg Fracture Risk Assessment Tool [FRAX]) can be used to estimate an individual patient’s risk of fractures with or without known bone densitometry scores.34 Reassessment of fracture risk is a critical first step before discontinuation of treatment is considered.29 If treatment is suspended, risk assessment should be repeated annually and treatment restarted if necessary.

Conclusion

Treatment adherence is influenced by multiple factors. The patient–provider relationship is critical through regular follow up and review of disease risk, progression, patient characteristics and preference, and treatment options. Patient education and understanding of disease and treatment risks and benefits is crucial in an asymptomatic disease. Reminder systems are useful where forgetfulness is a concern. Strategies to improve adherence include discussing novel drug formulations (eg delayed-
release enteric coating) and the use of parental options. This is evident in the shift to the preference for six-monthly denosumab over bisphosphonates. A clinician protocol for ongoing patient risk–benefit assessment and re-evaluation at each successive appointment is essential. Specific therapy-related barriers may be addressed on a case-by-case approach specific to each patient.

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References


