Compliance with treatment in osteoporosis patients

An ongoing problem

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BACKGROUND
Osteoporosis is a chronic condition that generally requires long term therapy with agents such as bisphosphonates, selective oestrogen receptor modulators, or hormone therapy for fracture risk reduction to be apparent. However, compliance with therapy in the 'real world' setting has generally been less than that seen in clinical trials.

OBJECTIVE
This article reviews the trends of compliance and persistence with bisphosphonate therapy in patients with osteoporosis in the 'real world' setting.

DISCUSSION
Studies in Australia and overseas have shown that once weekly administration of bisphosphonates improves compliance with treatment compared with a daily regimen. However, although patients prefer once weekly bisphosphonates over daily treatment, compliance and persistence remained suboptimal in many patients receiving once weekly therapy. The introduction of less frequent dosing regimens such as once monthly or once yearly may increase compliance.

Compliance can be defined as the extent to which a person's behaviour coincides with medical advice relating to dose and dosing interval.[1,2] Persistence refers to the continued renewal of prescriptions and adherence to the extent to which a patient follows a prescribed regimen of medication.[3]

The extent of noncompliance in chronic disease varies, but for many diseases 40–50% of patients do not persist with treatment beyond 12 months.[3] Noncompliance appears to be a consistent problem regardless of the underlying disease, symptoms, treatment regimen or patient's age,[4,5] and may result in negative outcomes for patients.[2] The reasons for noncompliance are multifactorial and are similar across various diseases (*Table 1*).

Doctors can enhance compliance and achieve desired outcomes by involving patients as partners in the management of their condition.[1,2] This enables patients to take a more active role in their treatment, which promotes compliance and enhances patient satisfaction and outcomes.

Osteoporosis

Osteoporosis is a significant public health problem in Australia. It was estimated that in 2001, approximately 2 million Australians were affected by osteoporosis, with a total cost burden of $7.4 billion per year.[6] This condition is more prevalent than hyperlipidaemia and incurs more years of healthy life lost than Parkinson disease, cervical cancer or rheumatoid arthritis.

Current treatments for osteoporosis including bisphosphonates, raloxifene, hormone therapy (HT) and parathyroid hormone have been shown to reduce the risk of fractures by 30–50% in clinical trials.[7] However, the efficacy found in clinical trials may not be replicated in the 'real world' setting because of poor compliance.[8]

A recent retrospective analysis of Australian Health Insurance Commission dispensing data for medications listed on the Pharmaceutical Benefits Scheme (PBS) for the year ending July 2004 has shown moderately high rates of discontinuation of treatments for osteoporosis (*Figure 1*).[9]

Only 57% of patients with osteoporosis persisted with treatment after 12 months. Furthermore, of those patients who discontinued therapy, the majority ceased taking treatment within the first 6 months.[9] Raloxifene exhibited a similar rate of discontinuation to that of the bisphosphonates over 12 months. However, calcitrol and etidronate had much greater rates of discontinuation. Once weekly bisphosphonates generally had lower discontinuation rates than those administered daily (*Figure 2*).

Table 1. Factors that affect compliance with medication

Disease	Drug related	Patient	Follow up	Others
Absence of symptoms	Prevention vs. treatment	Lack of social support	Time	Patient-doctor relationship
Long term therapy required	Adverse effects	Lack of disease knowledge	Cost	
No immediate advantage from therapy	Duration of treatment	Denial of illness	Difficulties of follow up	
Multiple morbidities	Complexity of regimen	Patients' own views about how they are best treated		
	Greater number of drugs	Patients' concerns about the value or appropriateness of taking medicines		
	Frequency of administration	Confusion or physical difficulties associated with taking medicine		
	Costs	Disruption to lifestyle or inconvenience		
	Access to medication			

Persistence with once weekly bisphosphonates after 1 year was slightly higher in the Australian data than that observed in studies conducted in Germany and the United States.[10,11] This may be due to the fact that in Australia, bisphosphonates are subsidised by the PBS for the treatment of osteoporosis in postmenopausal women with a prior fracture. Such patients may be more motivated to continue taking their prescribed medicine. Nevertheless, compliance remained suboptimal.

In terms of actual clinical practice, Van Staa et al[12] examined two databases containing medical records of medical practitioners in the United Kingdom and identified 12 373 patients who were commenced on either alendronate or risedronate. Of these, 54.6% used a daily dosing regimen and 45.4% weekly tablets. After 1 year, 63.6% of patients were compliant with treatment and 45.5% at 3 years. Treatment discontinuation was most likely to occur early in the course of treatment, whether daily or weekly, and predictors for noncompliance included age, sex, frequency of dosing and concomitant use of calcium and/or vitamin D. Daily bisphosphonate users were more likely to discontinue compared with weekly users (ratio of 0.87 [0.80–0.94]).

Bisphosphonates and osteoporosis treatment in Australia

Currently, bisphosphonates (Fosamax, Actonel, Didrocal) make up approximately 80% of the total units of the osteoporosis market in Australia[13] (defined as Evista 60 mg pack, Rocaltrol 0.25 µg pack, Sitriol 0.25 µg pack, Citrihexal 0.25 µg pack, Kosteo 0.25 µg pack, and Genrx Calcitriol 0.25 µg pack). Bisphosphonates are sometimes associated with adverse gastrointestinal effects, which may result in patients discontinuing treatment.[14] The requirement to remain upright for at least 30 minutes after oral administration can be inconvenient for patients, especially those taking daily therapy, and may reduce compliance.[15] It is possible that the availability of less frequently administered medications may improve compliance and persistence, and consequently efficacy, because of the potential for fewer adverse effects and greater convenience.[15]

Retrospective analyses of prescription claims from databases in the US and Germany have shown that treatment compliance and therapy persistence are significantly greater in patients with osteoporosis receiving once weekly regimens of bisphosphonates than in those receiving daily bisphosphonate therapy over 1 year.[10,11,16]

Compliance, as assessed by mean medication possession ratio (MPR: the proportion of days within the 1 year follow up for which patients were supplied therapy) was significantly higher in patients receiving once weekly bisphosphonates than in those receiving daily treatment (65% and 69.2% vs. 54% and 57.6%; $p<0.0001$).[11,16] Adequate compliance (defined as MPR ≥80%) was significantly higher in patients receiving once weekly bisphosphonates than in those receiving a daily regimen (30.6–55.3% vs. 19.4–40.4%; $p<0.05$). Patients receiving once weekly therapy had significantly

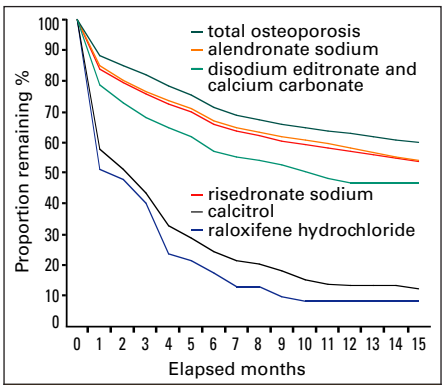

Figure 1. Continuation of osteoporosis therapy in Australia by agent

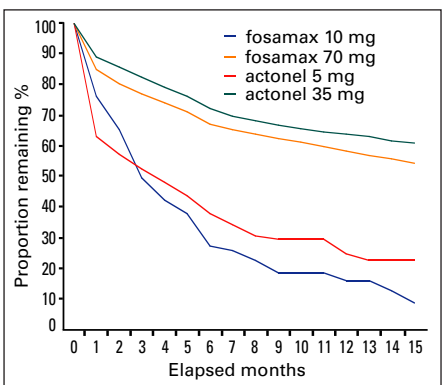

Figure 2. Continuation of once weekly and daily bisphosphonate therapy in Australia

longer persistence than those receiving a daily regimen (226.8 vs. 185.2 days; $p<0.001$).[16] After 1 year, more women with osteoporosis receiving once weekly bisphosphonates persisted with treatment than those receiving daily therapy (44.2% and 46.5% vs. 27.8% and 31.7%).[10,16]

Intermittent administration

In a randomised, open label, preference study, more patients preferred a once weekly dose of alendronate than a daily regimen.[17] This raises the possibility that less frequently administered dosage regimens may further enhance compliance and so maximise the therapeutic benefit of bisphosphonates. Two such regimens, namely once monthly ibandronate and once yearly zolendronate are likely to become available in the near future.

Once monthly or once yearly therapy?

Ibandronate is a potent, nitrogen containing bisphosphonate that can be administered orally with extended dosing intervals. In a study of 2946 women with postmenopausal osteoporosis, oral ibandronate given daily or intermittently (between dose interval of >2 months) reduced vertebral fracture risk at 3 years by 52% (daily) and 50% (intermittent), with both regimens having a similar safety profile to placebo.[18] Recently, once monthly oral ibandronate has been shown to be as effective as daily ibandronate.[19] A patient preference survey showed that 63% of women with osteoporosis receiving weekly bisphosphonate treatment would prefer treatment with a once monthly option.[20]

A once yearly formulation of zolendronic acid administered by intravenous injection has been developed and a phase II study has demonstrated that once yearly administration significantly increased bone mineral density in women with postmenopausal osteoporosis.[21] The results of a phase III study evaluating the effect of once yearly zoledronic acid on fractures should be available in the next few years.[22]

Conclusion

Poor compliance is multifactorial. Therefore, in the real world setting, it is important for doctors to adopt patient centred approaches to optimise compliance. Long term adherence to therapy is required for optimal therapeutic benefit for patients with osteoporosis. Numerous 'real life' studies have shown that although compliance has improved with weekly bisphosphonate regimens, it remains suboptimal. Less frequent regimens such as once monthly or once yearly administration may increase patient convenience and therefore potentially improve compliance and achieve the full potential benefit of bisphosphonate therapy.

Conflict of interest: Roche Pharmaceuticals commissioned Adrenalin Strategics to produce a first draft of the paper. Neither were involved in the final version.

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