

## Stopping medicines – bisphosphonates in postmenopausal osteoporosis

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The burden of osteoporosis and the associated morbidity and mortality is substantial. One in three women over the age of 50 is affected by the condition and nearly half of all women will experience a fracture by the age of 70.<sup>1</sup> Osteoporotic hip fracture is associated with a mortality of approximately 20%. Half of all survivors are left incapacitated and many fail ever to regain their previous levels of independence.<sup>2</sup>

Factors relating to a woman's risk of having a fracture are known and calculators exist to help to inform the decision to provide prophylaxis or treatment of disease, although the thresholds for this are still subject to some debate. Modifiable lifestyle factors should be addressed and calcium and/or vitamin D supplementation should be provided unless the clinician is confident that the woman has an adequate dietary calcium intake and is vitamin D replete.<sup>3,4</sup> For a woman diagnosed with osteoporosis, where the appropriate threshold is reached and the decision is made to implement prophylaxis or treatment, the first-line choice of medicine is alendronate.<sup>3,4</sup>

There has recently been considerable debate surrounding the required duration of treatment with bisphosphonates to produce the optimal antifracture activity without subjecting the patient to unnecessary treatment and its possible attendant adverse effects. To understand the debate it is necessary to briefly consider the mechanism of action and the nature and frequency of different adverse effects.

### Mechanism and duration of action

The potent, nitrogen-containing bisphosphonates exert their effect primarily by reducing osteoclastic bone resorption. They have different and unique profiles of affinity for binding to bone, which may be affected by various patient-specific factors, and this probably results in clinically meaningful differences in the speed of onset and offset of action.<sup>5,6</sup> However, in general, bone resorption is thought to be maximally reduced after 3 months of continuous oral therapy, or more quickly when a bisphosphonate is given intravenously.<sup>6</sup> Bisphosphonates with higher affinity bind strongly to the bone surface but are slower to spread throughout the bone; they are likely to exert their effects more slowly but continue to do so for longer after treatment is withdrawn. The precise biological half-lives of the various nitrogen-containing bisphosphonates in bone have not been well characterised, but are likely to be in the region of 10 years.<sup>6</sup>

(Etidronate is a less potent, non-nitrogen-containing bisphosphonate with a different mechanism of action; it is not considered to be a first-line bisphosphonate for the prophylaxis or treatment of postmenopausal osteoporosis.)

There is some evidence from a long-term trial that alendronate continues to influence bone mineral density (BMD) for some time after treatment is stopped.<sup>7</sup> However, there is little compelling evidence that this also equates to a decrease in fracture rate. The trial was not powered to demonstrate this and, due to the expense involved, it is unlikely that another will ever be done. There is some very limited evidence of a carry-over effect of risedronate in the year following its cessation.<sup>8</sup>

## Some reasons to consider stopping a bisphosphonate

Due to the serious consequences of a fracture, patients who meet the threshold for prophylaxis or treatment should not have their bisphosphonate discontinued without good reason. In many cases, such as true intolerance, treatment cessation would usually require a trial of another agent in the first instance.

### True intolerance

Various upper gastrointestinal disturbances are the most common adverse effects associated with bisphosphonate therapy. Occasionally these may be severe enough to warrant discontinuation of therapy (see below). However, it is useful to note that many studies have shown that the incidence of nausea, dyspepsia, abdominal pain, and gastritis does not significantly differ between oral alendronate, risedronate, and ibandronate and placebo. Thus, although such symptoms are common, both patients and health professionals may have become sensitive to the potential for their occurrence.<sup>6</sup>

NICE defines bisphosphonate true intolerance as persistent severe upper gastrointestinal disturbance warranting discontinuation, despite the correct dosing instructions being followed.<sup>3,4</sup> When a patient is taking concurrent calcium and/or vitamin D supplementation, it may be worth changing the supplement to establish if this is the cause of the gastrointestinal symptoms.

### Rare adverse effects

Bisphosphonates have been linked with some very rare adverse effects such as osteonecrosis of the jaw (ONJ) and atypical stress fractures.

When bisphosphonates are used orally for the treatment or prophylaxis of osteoporosis the incidence of ONJ is very low.<sup>9</sup> There is clear evidence to show that the condition is associated with the intravenous route and the higher doses used in cancer.<sup>9</sup> If a patient has poor dental status prior to initiation of therapy for osteoporosis, a dental check-up may help to minimise risk.

Atypical stress fractures may be associated with prolonged treatment with bisphosphonates but are exceedingly rare.<sup>10</sup> They are thought to be due to long-term bone turnover oversuppression, leading to poor bone remodelling and accumulation of microdamage, although a causal relationship is still the subject of some debate.<sup>5</sup> It is recommended that a patient developing such a fracture should discontinue treatment and receive no further bisphosphonates unless the benefits of treatment clearly outweigh the risks.<sup>11</sup>

### Medication "holiday"

Bearing in mind the risks and benefits of the bisphosphonates, there has been much discussion of the advisability of a medication holiday after a period of treatment.<sup>5,6,10,12,13,14</sup> The consensus of opinion at present is that there is a lag period following discontinuation during which bisphosphonates continue to exert some effect on BMD and certain patients may be able to stop treatment for a period without ill-effect. However, the data available to guide practice are limited and there are confounding issues – such as concordance – that complicate the issue. For example, more than 40% of patients discontinue their medication during the first year of therapy and approximately 75% of patients do so by 5 years; the possibility that a large proportion of patients will not take their bisphosphonate for long enough or consistently enough to derive prolonged benefit from treatment should be borne in mind.<sup>15</sup>

(The issue of non-compliance is important even when a medication holiday is not being considered. Medication reviews, opportunistic reviews when patients consult, and routine searches for defaulters may all help to identify patients who are not taking their medication as prescribed.)

The duration of treatment required before a medication holiday and the duration of the holiday period itself will be determined by fracture risk. Current opinion points towards those women at high risk of fracture (for example, T-score  $\leq -3.5$ , no improvement of T-score on treatment, previous fracture, high risk of falls, etc.) remaining on uninterrupted medication. For women at lower risk of future fracture (for example, T-score has improved to the osteopenic or normal range on treatment, no previous fracture, low risk of falls, etc.) it may be possible to stop treatment after a period of around five years. After stopping treatment it is recommended that lumbar spine BMD is monitored regularly, for example annually, and compared with previous results. (It is important to consider that results from different machines and testing centres may vary.) The bisphosphonate should be reinstated if there is a clinically significant decrease in BMD or if a fracture occurs.

### Limited life expectancy

It is recognised that when a medicine is unlikely to realise its potential benefit it should be stopped.<sup>16</sup> As discussed above, when alendronate is stopped it is probable that some residual effect on BMD remains for years after cessation, although it is uncertain how this affects fracture risk and whether this applies to other bisphosphonates. In frail, institutionalised, elderly patients, without previous fracture, calcium and vitamin D supplementation alone has been shown to decrease the rate of hip fracture.<sup>17</sup>

Note that supplementation alone has not been shown to reduce fracture rates in other populations. If a patient meets the criteria for treatment or prophylaxis, all but those with the most limited life expectancy should receive active therapy.

### Summary

- ◆ Osteoporotic fracture is associated with significant morbidity and mortality and osteoporosis should be treated appropriately.
- ◆ The half-lives of the various nitrogen-containing bisphosphonates are likely to be around 10 years and there is some evidence with alendronate of a continuing effect on BMD for some time after cessation.
- ◆ Non-compliance is a major issue with bisphosphonate therapy and this should be addressed whenever possible.
- ◆ A bisphosphonate should be stopped in the case of true intolerance or serious adverse effects.
- ◆ Consideration may be given to stopping bisphosphonates either temporarily or permanently in some patient groups.

### References

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