Once-weekly treatment for osteoporosis

Mike Stone

Daily oral bisphosphonates are a well-established treatment option for osteoporosis. However, many patients find the daily dosing regimen inconvenient. Once-weekly alendronate offers greater convenience to patients while providing equal efficacy.

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Osteoporosis is a progressive disease, characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (*Figure 1*). The disease is a major burden on the NHS, leading to 200 000 fractures annually (Royal College of Physicians and Bone and Tooth Society, 2000). Osteoporotic fractures often result in pain, disability and the need for long-term care, and result in an estimated cost of £1.7 billion per year (Torgerson et al, 2001). Unsurprisingly, better management of the disease is rising up the agenda of the government, national bodies such as the Royal College of Physicians and regional health authorities.

TREATMENT OPTIONS FOR MANAGEMENT OF OSTEOPOROSIS

The main objective of osteoporosis treatment is to prevent fractures (or further fractures). There are a number of treatment options available, all of which have different effects on fracture reduction at various sites of the skeleton.

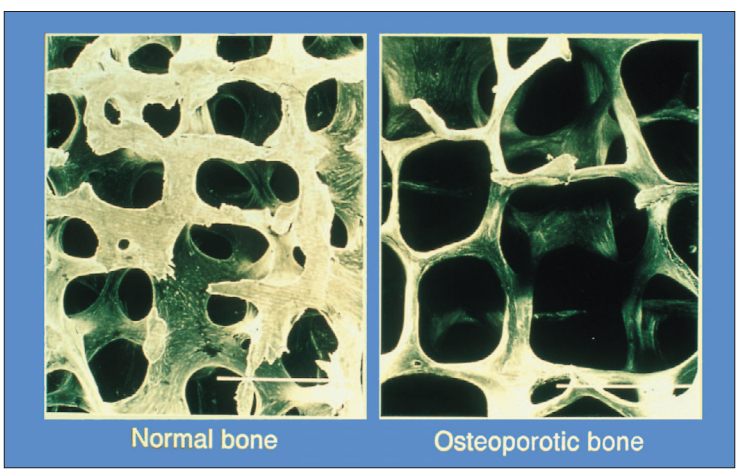

Figure 1. Electron micrograph of normal and osteoporotic bone.

An evidence-based review of treatment options was published by the Royal College of Physicians (1999) and updated in the Royal College of Physicians and Bone and Tooth Society guidelines (2000). The first-line treatment choices for osteoporosis in active patients are bisphosphonates, hormone replacement therapy or a selective oestrogen receptor modulator. Calcium and vitamin D represent a further treatment option in frail elderly patients. Key considerations affecting choice of treatment include age, severity of the disease and likely compliance.

ONCE-WEEKLY DOSING: AN INNOVATION

The first ever once-weekly treatment for osteoporosis is now available, representing an important advance in the treatment of the condition and offering new benefits to patients and prescribers. The well-established bisphosphonate, alendronate (Fosamax, Merck Sharp & Dohme Limited, Hoddesdon, Herts), is available as a once-weekly dose, which delivers the same clinical benefits of the daily treatment, but with the convenience of once-weekly administration. Alendronate once weekly 70 mg is licensed for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fractures.

BENEFITS OF ONCE-WEEKLY DOSING

Once-weekly dosing offers a number of potential benefits over existing treatment options for preventing fractures. Although highly effective at increasing bone mineral density (BMD), some patients find the administration of daily oral bisphosphonates troublesome. All bisphosphonates must be taken with a glass of water on an empty stomach, with the patient remain-

ing upright for a minimum of 30 minutes following administration.

In addition to being more acceptable to patients, perhaps the most important benefit of once-weekly dosing is the potential for improved compliance. Compliance is a major challenge in all chronic diseases. It has been estimated that around 50% of patients with a chronic disease do not take their medication in fully therapeutic doses and so do not derive the optimal benefits of treatment (Working Party of the Royal Pharmaceutical Society of Great Britain, 1997). The consequences of poor compliance impact on the patient, for example, through continuing illness and premature death, and on the NHS, with the need for increased health service expenditure on treating the avoidable consequent morbidity (Working Party of the Royal Pharmaceutical Society of Great Britain, 1997).

A number of factors have demonstrated improved compliance with treatment. Both educational interventions (i.e. information-giving) and behavioural interventions (i.e. taking account of the patient's lifestyle and tailoring the medication regimen accordingly) have been suggested as measures to improve compliance (Working Party of the Royal Pharmaceutical Society of Great Britain, 1997). Once-weekly alendronate responds to such factors with a simpler treatment regimen which is far less disruptive to patients' everyday patterns of living and a calendar packaging system with reminder stickers for use in personal calendars or diaries.

MECHANISM OF ACTION

Once-weekly dosing with alendronate is made possible by a combination of the biology of bone remodelling and the mechanism of action of bisphosphonates. Skeletal bone is constantly in a state of flux, with old bone being resorbed and new bone being formed (a process called remodelling). Osteoporosis occurs when the balance of bone formation and resorption by the body is upset, leading to a deficit of bone building and a weakening of the skeleton. Alendronate works by reducing the amount of bone resorbed during each remodelling cycle, so that resorption does not exceed formation and there is a net increase in bone.

The resorption phase lasts for about 2 weeks, but because alendronate remains at the bone surface for several weeks, administration of the treatment even on a weekly basis should sustain drug levels at all sites where remodelling is taking place (Bone et al, 2000) (*Figure 2*).

Preclinical studies have shown that at dosing intervals of less than 2 weeks, the magnitude of the benefit on BMD is related primarily to the cumulative amount of alendronate administered, rather than to the frequency of administration.

ESTABLISHED CLINICAL PROFILE OF ALENDRONATE

Daily alendronate has been extensively studied and has a well-established clinical profile. There is a strong consistency in efficacy across all alendronate studies, indicating that the treatment increases BMD at the spine by about 5% and the hip by about 3% (Liberman et al, 1995; Pols et al, 1999). The response rate with alendronate is high, with 96% of patients showing an increase in lumbar spine BMD after 3 years (Liberman et al, 1995).

Alendronate also results in a significant reduction in the risk of fractures (Black et al, 1996; Pols et al, 1999). In a study of postmenopausal women with low bone mass (Fosamax International Trial; FOSIT), alendronate reduced the risk of non-vertebral fractures by 47% (P=0.021) (Pols et al, 1999). In post-menopausal women with existing vertebral fractures (the vertebral arm of the Fracture Intervention Trial; FIT), alendronate reduced the risk of fractures at the hip, wrist and spine by about 50% (vertebral fracture: P<0.001; hip fracture: P=0.047; wrist fracture: P=0.013), and reduced two or more vertebral fractures by 90% (P<0.001) (Black et al, 1996).

The benefits of daily alendronate are observed soon after the treatment is initiated. In the FOSIT study, alendronate produced significant increases in hip and spine BMD within 3 months (P<0.001) (Pols et al, 1999). A new analysis of FIT has shown that alendronate

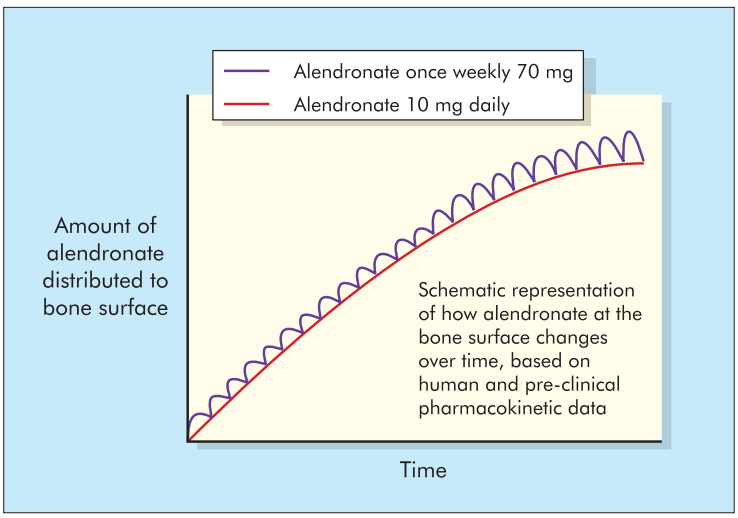

Figure 2. Skeletal accrual of daily and once-weekly alendronate (Porras et al, 1999; Bone et al, 2000).

reduces the risk of vertebral fracture by 59% by the end of the first year of treatment ($P<0.001$) (Black et al, 2000).

The risk of hip fracture was shown to decrease by 63% at 18 months ($P=0.014$) (Black et al, 2000).

Once achieved, statistically significant benefits were maintained throughout the 3-year study period.

EQUIVALENCE TO THE DAILY FORMULATION

Once-weekly alendronate has been studied in a large randomized controlled trial exploring equivalence with the once-daily formulation (Schnitzer et al, 2000). The 1-year, double-blind, multicentre study compared the efficacy and safety of 70 mg alendronate once-weekly with the 10 mg daily regimen in post-menopausal women with osteoporosis (Schnitzer et al, 2000). The once-weekly regimen produced equivalent increases in lumbar spine BMD compared with alendronate 10 mg daily (*Table 1*). Similar increases were seen in total hip and total body BMD and equivalent reductions in biochemical markers of bone resorption and bone formation were also observed (Schnitzer et al, 2000).

TOLERABILITY OF ONCE-WEEKLY ALENDRONATE

Once-weekly alendronate is well tolerated and may have the potential for improved tolerability compared to the daily formulation. In the equivalence study comparing the safety and efficacy of weekly and daily administration, all doses of alendronate were observed to be well tolerated. However, once-weekly alendronate was associated with significantly fewer serious upper gastrointestinal side effects compared to the once-daily regimen ($P=0.012$) (Schnitzer et al, 2000). These findings are in line with other data which suggest that tolerability is related to the frequency of administration rather than the dose itself (Bone et al, 2000).

TABLE 1.
Per cent change from baseline in bone mineral density at month 12 in patients treated with alendronate 10 mg daily and alendronate 70 mg once-weekly

Site	10 mg daily at 12 months	70 mg weekly at 12 months
Spine	5.4	5.1
Total hip	3.1	2.9
Femoral neck	2.9	2.3
Trochanter	4.4	3.9
Total body	1.0	1.0

All changes are significant increases from baseline ($P<0.05$). From Schnitzer et al (2000)

KEY POINTS

- Once-weekly alendronate is well tolerated.
- Once-weekly alendronate has equal efficacy to once-daily alendronate.
- This formulation offers greater convenience to patients.

CONCLUSION

The new once-weekly formulation of alendronate provides clinicians with an important new option when managing patients with osteoporosis to prevent fractures. Not only does the formulation provide equal efficacy to the daily dose, but it is likely to offer much greater convenience to patients. There may also be important additional benefits in terms of improved compliance and tolerability. HM

Conflict of interest: Dr Stone has acted as an adviser to Merck Sharp Dohme Pharmaceuticals and received honoraria for educational talks.

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