How alendronate became the most widely used bisphosphonate in the UK

Continuing with our monthly articles on landmark drugs, Jenny Bryan takes a look at how alendronate was shown to reduce both vertebral and non-vertebral fractures, which gave it an advantage that etidronate and other early bisphosphonates were not able to match.

This month’s landmark drug, alendronate (Fosamax), developed by Merck Sharp and Dohme, was not the first bisphosphonate to be launched in the UK for the treatment of osteoporosis. But it soon became the most widely used in a rapidly expanding market and, 15 years later, the vast majority of women with osteoporosis are still prescribed cheap generic versions of the drug.

Much of this success can be attributed to a series of large trials that Merck started in 1990 to provide outcomes data for alendronate that would trump that of its rivals.

“Initially most of the clinical studies of bisphosphonates focused on their effects on bone mineral density,” explains Tim Spector, consultant rheumatologist and professor of genetic epidemiology at Guy’s and St Thomas’ Hospital and King’s College London. “But Merck took things forward by showing that alendronate reduced fractures, initially vertebral fractures, but later hip and other non-vertebral fractures. This gave it an advantage which etidronate and the other early bisphosphonates weren’t able to match.”

Early origins

The bisphosphonates (or diphosphonates as they were at one time called) are synthetic analogues of inorganic pyrophosphate, and were first produced in the middle of the 19th century for use in the textile, fertiliser and oil industries.1

It was not until the mid-1960s that bone metabolism specialist Herbert Fleisch and colleagues at the University of Berne, Switzerland, showed that, like pyrophosphate, bisphosphonates inhibited the crystallisation and dissolution of calcium phosphate crystals in vitro,2 which led the team to suggest that the compounds might act on bone resorption in vivo.

Subsequent research has shown that, in vivo, bisphosphonates have a specific affinity for bone tissue, where they reduce bone resorption by inhibiting recruitment and activity of osteoclasts and shortening their lifespan.

There is evidence that non-nitrogenous bisphosphonates, such as etidronate, clodronate and tiludronate, which most resemble pyrophosphate in structure, are incorporated into the phosphate chain of adenosine triphosphate, making it unusable for energy production in osteoclasts, which then die.1

In contrast, nitrogen-containing bisphosphonates, such as alendronate, ibandronate and risedronate, block the enzyme farnesyl diphasphate synthase in the HMG-CoA reductase pathway to prevent formation of key isoprenoid lipids in osteoclasts.

These lipids are essential to anchor proteins to cell membranes and, without them, normal cell function is sufficiently impaired to result in cell death.

From laboratory to clinical trials

In an early clinical study in patients with corticosteroid-induced osteoporosis, the first bisphosphonate to market, etidronate, was shown to increase metacarpal and vertebral bone mineral density (BMD),3 and this was subsequently shown to translate into a reduction in vertebral fractures of up to 88 per cent in the second and third years of intermittent cyclical treatment.4

Osteoporotic spongy bone: bone mineral density increases in the spine and hip were reported after only three months of alendronate treatment in the Fosamax International Trial (FOSIT) (Steve Gschmeissner/Science Photo Library)
“Bisphosphonates are amazing value for money and, if you take them regularly, they will reduce your fracture rate by 30 to 50 per cent”

By this time, Merck had demonstrated that alendronate also inhibited bone resorption, and embarked on dose-ranging studies of the effects of the drug on BMD and vertebral fractures in women with post-menopausal osteoporosis. These confirmed that, after three years, alendronate reduced the proportion of women with new vertebral fractures by 48 per cent, decreased progression of vertebral deformities and reduced loss of height.1 Merck then leap-frogged its competitors by embarking on the massive Fracture Intervention Trial (FIT) with nearly 6,500 women with low BMD, a third of whom had already had a vertebral fracture. All the women were prescribed daily calcium and alendronate 5mg per day, which was increased to 10mg per day after two years, following results of other studies showing that the higher dose was more effective.

After three years, morphological vertebral fractures were reduced by 47 per cent (P=0.01) in women with previous vertebral fractures, and clinical vertebral fractures were down by 55 per cent (P<0.01) in women with previous vertebral fractures, and clinical vertebral fractures were down by 55 per cent (P<0.01). But what swung it for Merck was that non-vertebral fractures, and clinical vertebral fractures were down by 55 per cent (P<0.01), together with a 41 per cent reduction in hip fractures (P=0.002).9

But research by Professor Spector and colleagues suggests that not all patients are in favour of infrequent dosing.10 Their study of nearly 2,500 patients showed that 45 per cent preferred to take daily medication for osteoporosis, while one in five preferred weekly and 30 per cent preferred monthly therapy. “In general, younger patients prefer to take their treatment less regularly, but older ones like the routine of daily treatment. But if patients are taking many different drugs — as a lot of older patients are — then there is still a place for bisphosphonates that only need to be taken once or twice a year,” says Professor Spector.

Market closed?

In the past, bisphosphonate manufacturers have benefited from the demise of hormone replacement therapy for osteoporosis prevention following concerns about the increased risk of breast cancer. But Professor Spector believes that HRT was never really competition for the bisphosphonates.

“HRT never had the same impact on fracture rates as bisphosphonates because women wouldn’t stay on it when they needed it most. They’d take it in their 50s and 60s, but didn’t want to continue into older age. So, within a short time of stopping HRT, they’d get fractures,” he explains.

Although critical of some aspects of the National Institute for Health and Clinical Excellence osteoporosis guidance, Professor Spector supports the focus on the over-65s, who are at greatest risk of fractures, rather than the younger “worried well”. However, he points out that many women in their early 70s who have had fractures are still not prescribed bisphosphonates, and other high-risk groups, such as those on long-term systemic corticosteroid treatment, are also missing out.

The introduction of strontium ranelate and the recent European approval for the receptor activator for nuclear factor-κB ligand (RANKL) inhibitor, denosumab, are broadening the range of options for osteoporosis treatment, but Professor Spector does not expect any more bisphosphonates: “They’re amazing value for money and, if you take them regularly, they will reduce your fracture rate by 30 to 50 per cent. But I can’t see any more bisphosphonates being added to the range because they couldn’t compete on price. At £30 per year — less than the cost of calcium — it’s no wonder that NICE loves them.”

References


