

## Treatment of Paget's Disease

a report by

**David J Hosking**

Director, Metabolic Bone Disease Service, City Hospital, Nottingham

Bisphosphonates have revolutionised the treatment of Paget's disease since they were first introduced into clinical practice over 30 years ago.<sup>1</sup> Their ability to control the increased bone resorption of metabolic bone diseases such as Paget's disease depends on their ability both to bind to bone and to inhibit key cellular processes in the osteoclast.

Successive modifications of the basic bisphosphonate structure have increased the ability of these compounds to inhibit osteoclastic bone resorption. This is due to enhanced effects on critical cellular processes, as well as the development of physicochemical characteristics, which optimises their binding and retention within the skeleton. While the earlier bisphosphonates (etidronate, clodronate and tiludronate) exerted their effects through the formation of toxic complexes with adenosine triphosphate (ATP),<sup>2</sup> the newer nitrogen-containing compounds inhibit the key enzyme farnesyl diphosphate synthase in the mevalonate pathway.<sup>3,4</sup> This blocks the prenylation of small GTPase signalling proteins that are critical to the function of the osteoclast ruffled border. This results in a reduction in bone resorption, and since bone formation is coupled to resorption, the effect is to reduce both bone resorption and formation.

Modification of the R2 side chain by increasing the chain length or adding a nitrogen moiety increases the ability to inhibit farnesyl diphosphate. *In vitro* studies showed that the activity of recombinant farnesyl diphosphate was inhibited in decreasing order of potency: zoledronic acid > risedronate > ibandronate > alendronate > pamidronate.<sup>3</sup> The practical importance

of these observations is that the amount of bisphosphonate that has to be administered to achieve the desired control of bone turnover can be reduced, and this opens up the potential for intravenous administration.<sup>5</sup> This option is of considerable practical importance, since bisphosphonates as a class are poorly absorbed from the upper small intestine and need to be taken while fasting.<sup>6</sup> Moreover, they have the potential to irritate the lower oesophagus, which entails careful adherence to the mode of administration.<sup>7</sup> These requirements adversely affect compliance, which is well shown in surveys of bisphosphonate therapy in osteoporosis.<sup>8,9</sup> Modification of the basic bisphosphonate structure has also resulted in greater adherence of the bisphosphonates to hydroxyapatite.<sup>10,11</sup> *In vitro* testing shows that the binding affinities of bisphosphonates to hydroxyapatite can be ranked in decreasing order: zoledronate > alendronate > ibandronate > risedronate > etidronate > clodronate.<sup>10</sup> This is of clinical importance as it results in greater persistence of the effect on bone remodelling once treatment has been completed.

### Bisphosphonates in Clinical Use

In clinical practice, the essential requirements for effective treatment of Paget's disease are potency, persistence and compliance. Although the cellular effects and physicochemical properties of the various bisphosphonates can be isolated and compared by *in vitro* testing, their *in vivo* effect also depends on variables such as bone turnover and renal function.<sup>12</sup> There have been three phases of bisphosphonate development, beginning with etidronate, clodronate and tiludronate,

David J Hosking is a Consultant Physician and Director of the Metabolic Bone Disease service at the City Hospital, Nottingham, UK, and until recently was also Professor of Mineral Metabolism in the Department of Biochemistry at the University of Nottingham. He is currently a Visiting Professor at the University of Zagreb, Croatia, and an examiner for the Royal College of Physicians of London. He received his medical training at the University of Birmingham Medical School, Birmingham, UK, and Post-graduate training in Leiden, Netherlands. Among previous appointments, he has held posts as Clinical Director of Medicine and Director of Research and Development at City Hospital, Nottingham. He has published widely in the areas of Paget's disease, osteoporosis, calcium metabolism and bisphosphonates. He is a member of the Editorial Board of *Osteoporosis International*, the Scientific Advisory Group of the National Association for the Relief of Paget's Disease, the Paget's Foundation in US (from whom he received the J B Johnson Award for services to Paget's disease) and the National Osteoporosis Society (UK).

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which at the time represented huge advances in treatment. This was followed by the development of the nitrogen-containing compounds pamidronate, risedronate and alendronate, and finally by the introduction of zoledronate. Most of these compounds were first tested against placebo to confirm their inhibitory effect on bone resorption. These clinical studies encompassed a wide range of disease activity, making comparison between successive drug developments quite difficult. Direct studies between agents are more useful in determining clinical use and bilateral comparisons are available for most compounds. Although the main emphasis of these clinical trials was on potency, they all contributed to the understanding of the treatment of Paget's disease. *Detailed analysis of each bisphosphonate can be found in the online version of this publication.*

### Aims of Treatment

The ability to control bone turnover in very active Paget's disease and maintain suppression after a single dose for prolonged periods makes it important to revisit the aims of treatment. The main clinical features of the disease are bone pain, deformity and fracture,<sup>13,14</sup> and although there is some objective evidence linking control of bone turnover with relief of bone pain, there remains much subjectivity and a high placebo response.

Clinical symptoms, particularly pain, are often non-specific and it is important to define the distribution of Paget's disease in order to separate pagetic from non-pagetic complaints. Pain in Paget's disease is also present at rest, while that from osteoarthritis is only apparent on weight-bearing and tends to improve with rest. Deformity in Paget's disease<sup>15</sup> develops too slowly to be useful in the evaluation of specific anti-resorptive therapy. While it is well recognised that fracture risk is increased,<sup>16</sup> the true incidence is poorly characterised because of uncertainty about the size of the asymptomatic population of undiagnosed patients from which fracture cases are drawn.

Bone turnover measurements can be used as a surrogate for clinical effectiveness since they are more objective. As bisphosphonates have become more effective, the goal of treatment has shifted away from the percentage decrease in disease activity to the proportion of patients who achieve a bone turnover in

the lower part of the reference range. The reason for this is the demonstration that the duration of biochemical remission is strongly determined by the nadir value achieved by treatment.<sup>17</sup> It also seems reasonable to suppose that the risk of long-term complications, such as fracture, deformity and degenerative joint disease,<sup>18</sup> might be reduced by sustained control of bone turnover.

Although most patients respond to bisphosphonate therapy with a decrease in bone turnover, some do not show the expected response and this raises the issue of treatment resistance. In some cases this might simply be due to inadequate dosage or potency of the bisphosphonate, but occasionally true resistance may occur. The mechanism of this effect is uncertain, but was well shown by a study using equipotent doses of oral alendronate and intravenous pamidronate where previously untreated patients behaved similarly to the two bisphosphonates. In those patients previously treated with pamidronate, the response to re-treatment was less complete compared with those treated for the first time with alendronate. The cellular processes that underlay the decrease in responsiveness and the reason why this should appear to be specific to a particular bisphosphonate is unclear. It could conceivably relate to the physicochemical properties of individual bisphosphonates, where initial adsorption to hydroxyapatite might influence subsequent binding through changes in the zeta potential.

In the recent zoledronic acid trial, previous bisphosphonate-treated patients relapsed to a greater extent compared with those who were previously untreated prior to the trial.<sup>19</sup> This latter situation may be different from resistance and is quite complex, since factors other than the nadir level of bone turnover influence relapse.<sup>17</sup> These include extent of disease and pre-treatment activity, as well as dose of bisphosphonate. An interesting possibility with the use of potent bisphosphonates, such as zoledronic acid, that achieve normal bone turnover in the majority of patients may be the prevention of resistance. ■

*A longer version of this article can be found in the Reference Section on the website supporting this briefing ([www.touchbriefings.com](http://www.touchbriefings.com)).*

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