Zoledronic acid in Paget's disease

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Paget's disease is characterized by increased bone turnover, and treatment has been revolutionized by the introduction of bisphosphonates. Zoledronic acid is the latest compound to be introduced into clinical practice. It has increased potency in terms of inhibiting critical enzymes needed for osteoclastic bone resorption. This means that small amounts of the drug can be given as a 15-min intravenous infusion with the potential for improved compliance compared with oral therapy. The strong adherence of this bisphosphonate for hydroxyapatite results in prolonged control of bone turnover/disease activity. Recent clinical trials comparing the effect of a 5-mg infusion of zoledronic acid with oral risedronate 30 mg for 2 months showed rapid control of bone turnover in almost 90% of patients treated intravenously. Control of bone turnover persisted in an (ongoing) extended observation study for up to 24 months after the initiation of treatment. Most patients treated with zoledronic acid experienced little increase from the post-treatment nadir bone turnover. The hope is that the ability to control Paget's disease in the long term will reduce the risk of long-term complications. It will also facilitate the shift of long-term management from secondary to primary care. The reduced requirement for re-treatment also makes this bisphosphonate a cost-effective drug of first choice for the treatment of Paget's disease.

Paget's disease is a common metabolic bone disease characterized by greatly increased focal bone remodeling [1]. It is primarily an abnormality of the osteoclast, but because bone resorption and formation are coupled, this leads to a secondary increase in osteoblast activity. Although many patients are asymptomatic, the disease can cause bone pain, fractures and deformity. It is also of great interest to the pharmacologist because it provides an excellent model for testing new antiresorptive drugs. As a consequence, most of the new bisphosphonates that have been introduced into clinical practice have first been studied in Paget's disease in order to evaluate their antiresorptive potential. The recent large trial of the use of zoledronic acid in Paget's disease confirmed the potency [2] and prolonged duration of action [3] of this new bisphosphonate, but also gave interesting insights into the mechanism of action of these agents in states of increased bone turnover. While this is interesting for the pharmaceutical industry, it is also good news for patients, who can now expect excellent control of their disease, which can be maintained in the long term with the potential to avoid long-term complications.

Keywords: bone turnover, Paget's disease, remission, risedronate, zoledronic acid

Pharmacology of zoledronic acid

Modification of the aminobisphosphonate structure has increased the ability of these compounds to inhibit the key enzyme, farnesyl diphosphate synthase, in the mevalonate pathway [4,5]. This blocks the prenylation of small GTPase signaling proteins, which are critical to the functioning of the osteoclasts' ruffled border and, subsequently, to bone resorption. Since bone formation is coupled to resorption in the remodeling cycle, the effect is to reduce both bone resorption and formation. The changes to the nitrogen-containing side chain also seem to increase the affinity of the bisphosphonate for hydroxyapatite, with the consequence that increased potency often seems to be accompanied by prolonged retention within bone [6]. *In vitro* testing shows that the binding affinities of bisphosphonates can be ranked in decreasing order: zoledronate > alendronate > ibandronate > risedronate > etidronate > clodronate [6], while their activity on recombinant farnesyl diphosphate shows a similar, but not identical, order of potency: zoledronate > risedronate > ibandronate > alendronate > pamidronate [4].

The significance of these changes is that the amount of bisphosphonate that is needed to control bone turnover is small enough to make it safe to be given intravenously [7]. This is an advantage because bisphosphonates are poorly absorbed from the upper small intestine, and need to be taken while fasting [8]. They may also irritate the lower esophagus, which therefore requires careful adherence to the mode of administration [9]. Both of these requirements adversely affect compliance.

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Treatment of Paget's disease: pivotal clinical trials

Potency: control of increased bone turnover

Experience with zoledronic acid is based on the pooled results of two identical protocols, which recruited 357 Pagetic patients from North America, Europe, South Africa and Australasia [2,3]. The trial compared the effects of a single 15-min infusion of zoledronic acid 5 mg with a 2-month course of oral risedronate 30 mg. The principal outcomes of the trial were the ability to control bone turnover, persistence of this effect over a period of years, and safety. These data have been reviewed extensively elsewhere [10]; this paper considers the clinical importance of these findings in more detail.

The strength of the efficacy study, particularly the ability to show clinical benefit, was largely dependent on the size of the trial and the inclusion of a large cohort of patients with very active disease, some with an alkaline phosphatase (ALP) level of more than 20-times the upper limit of normal [2]. While many previous trials have assessed response in terms of the percentage reduction in bone turnover (usually serum ALP), the zoledronic acid trial also provided information on the proportion of patients achieving normal bone turnover. This is much closer to the more demanding responses currently required in clinical practice, which often aim for a bone turnover around the midpoint of the reference range.

Normal serum total ALP was achieved in 89% of patients treated with zoledronic acid at 6 months. This reflects the high affinity of the bisphosphonate for bone mineral and its powerful inhibitory effect on farnesyl diphosphate synthase and bone resorption. Comparable responses for risedronate ranged from 43 to 68% in the two components of the trial and are similar to previous studies in Paget's disease with this bisphosphonate [11–13].

The ability to administer a single effective dose as a short infusion, rather than as a daily oral treatment spread over 2 months, unsurprisingly results in a more rapid control of bone turnover. This may be clinically useful in Paget's disease because early reversal of intense lytic areas in weight-bearing bones may reduce the risk of fracture. Although some neurological symptoms, such as spinal cord compression, may be due to bone overgrowth, there is often an element of vascular 'steal', due to increased bone blood flow, which is known to be rapidly reduced by antiresorptive therapy. A rapid fall in bone turnover also makes it easier to assess response and plan further treatment in the small number of cases with very active disease, who may need more than one infusion to achieve complete control. Earlier biochemical responses are also useful for the patient, who can anticipate clinical improvement knowing that the disease is coming under control.

Although the primary defect in Paget's disease is an increase in bone resorption with a secondary (coupled) increase in bone formation, the primary end point of the trial was the reduction in serum total ALP, since this is the measure most commonly used to assess Paget's disease in routine clinical practice. However, the trial also explored the use of a variety of other bone turnover markers and this is important when selecting the most sensitive indicator of response. The pattern of change in the N-terminal propeptide of type I collagen (PINP), another bone formation marker, was similar to that of ALP; however, the mean value fell further into the lower part of the reference range, probably because it is a more specific indicator of osteoblastic activity. Bone resorption markers, serum βC-telopeptide of type I collagen (βCTX), and the urinary excretion of αC-telopeptide of type I collagen (αCTX) showed a rapid decline, reaching a minimum value at 10 days, with partial recovery into the upper part of the reference range. The overall pattern of response was similar for both bisphosphonates, but the rapidity and magnitude of change was much greater for zoledronic acid compared with risedronate. Most of the patients treated with zoledronic acid had post-treatment values of ALP that clustered around the mid-normal value, with a substantial number in the lower half of the reference range. Although all patients treated with zoledronic acid showed a substantial response, those with very active disease did not achieve normal turnover. However, of the patients with an ALP up to ten-times the upper limit of normal, only eight of the 182 patients failed to achieve an ALP below the upper limit of normal. In clinical practice, as opposed to a clinical trial, these patients would be treated with a second infusion in order to reach the target bone turnover. By contrast, just under half of the patients treated with risedronate failed to achieve a normal ALP at 6 months, with a much smaller proportion achieving values in the lower part of the reference range.

The ability of treatment to reduce bone turnover to well within the normal range presents a substantial challenge to biochemical monitoring.

Experience with the limited skeletal involvement of monostotic Paget's disease showed that total ALP was a less sensitive marker than bone-specific ALP (bone ALP), PINP and the N-telopeptide of type I collagen (NTX) [14,15]. Although this issue has not been systematically explored, a similar approach to monitoring post-treatment turnover within the reference range would seem to be appropriate.

Persistence within bone: duration of remission

The second part of the study, by Hosking and colleagues, examined the ability of zoledronic acid and oral risedronate to maintain long-term control of bone turnover [3]. It included all of those patients in the efficacy paper who achieved a therapeutic response (normalization or >75% reduction in the total ALP excess above the midpoint of the reference range). The period of extended observations started 6 months after the first day of the initial therapy and continued for 18 months. The importance of persistence of remission is that it offers the potential to reduce the risk of chronic complications such as deformity, fracture and degenerative joint disease.

The greater potency of zoledronic acid resulted in a larger remission group (152 out of 169) being followed compared with risedronate (115 out of 127). During this extended observation period no bisphosphonate therapy was given, although supplements of calcium/vitamin D were continued. Long-term remission depends on both the potency of the administered bisphosphonate and the amount retained within the skeleton, and it is here that zoledronic acid and risedronate may differ substantially. Zoledronic acid has a high affinity for hydroxyapatite binding, whereas risedronate is much less adherent, and this will have an important effect on the duration of remission [6]. Although bisphosphonates are retained unchanged within bone, they have no effect on the remodeling cycle unless they are on the surface of the trabeculae. However, with time, the buried bisphosphonate may re-exert an effect when it becomes exposed by subsequent remodeling.

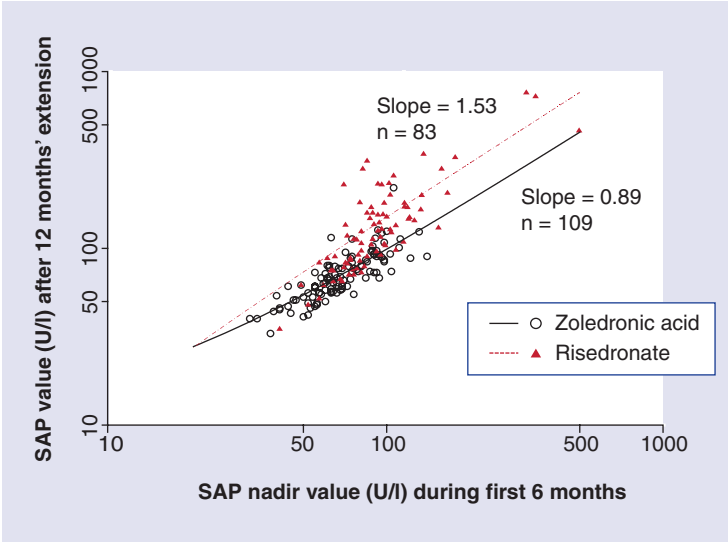
Previous studies with olpadronate, another potent intravenous bisphosphonate, showed that the major determinants of the duration of remission were the dose administered, the disease extent (number of affected bones), disease activity (number of previous therapies) and the post-treatment nadir serum ALP [16]. The effects of dose and the number of affected bones were not examined in the zoledronic acid studies but were indirectly addressed by the efficacy study [2]. However, it is possible to separate the effects of drug potency from that due to the post-treatment nadir bone turnover, as illustrated in **Figure 1**. This shows a plot of individual values of serum ALP at 6 and 24 months after the start of treatment. For clarity, only those values within the reference range are shown. It can be seen that for any given post-treatment value at 6 months, the ALP at 24 months changed less in those treated with zoledronate compared with those given risedronate. This shows that, after matching for nadir bone turnover, there is residual benefit from zoledronate therapy. Clearly, potency is a component. Skeletal retention will also contribute to this, although it cannot be separately quantified without using different doses. The amount of bisphosphonate taken up during treatment depends on disease activity [17], but this was well matched in the initial study and will not be an important factor apart from the issue of hydroxyapatite adherence. Thus, both potency and skeletal retention are important characteristics of zoledronic acid, which result in the achievement of sustained control of bone turnover within the normal range.

An additional interesting observation was that, in patients treated with zoledronic acid, the duration of remission was uninfluenced by the presence or absence of previous bisphosphonate treatment. By contrast, the treatment-naive patients receiving risedronate seemed to have a more prolonged remission. It is unclear at the present time whether this is just a reflection of potency or whether a more qualitative change in osteoclast responsiveness is involved.

Clinical benefit & quality of life

The strength of this trial was the large number of patients with very active disease who responded to treatment with a marked reduction in bone turnover. This allowed evaluation of clinical end points, which were measured using eight components of the short form general health survey (SF-36). This provides a comprehensive way of measuring health from a patient's point of view by scoring standardized responses to standardized questions. The physical and mental component summaries are both derived from SF-36 responses and have been validated as assessments of physical functioning

Figure 1. Individual values of serum alkaline phosphatase at 6 and 18 months postinitiation of treatment.



Only those values within the reference range are shown for clarity.
The complete data set is shown in [3].
SAP: Serum alkaline phosphatase.

and mental health. The brief pain inventory short form was originally developed to measure the severity of cancer pain and its effect on patients' functioning, but it has also been validated in other diseases. The SF-36 was developed for clinical trials where multiple assessments of pain are required.

Quality of life (QoL) scores tended to improve with zoledronic acid but were more mixed in those treated with risedronate. At 3 months there were statistically significant improvements in physical functioning, bodily pain and the physical component summary scores in those patients treated with zoledronic acid, while at 6 months there was a significant improvement in general health and the physical component summary scores. The important observation here was that all of the QoL domains showed a trend towards improvement with zoledronic acid, while this was not so for risedronate. This suggests that there was a significant difference between the clinical outcomes of these two types of bisphosphonate treatment and supports the view that the greater the reduction in bone turnover, the greater the probability of associated clinical benefit.

The limitations are that this protocol did not include a placebo arm, so the changes in pain and gait speed produced by the two bisphosphonates are more difficult to confirm compared with studies of an active bisphosphonate and placebo. In addition, the trials recruited patients on the basis of biochemical disease activity and not on clinical symptoms. As a consequence, many of the patients who had biochemically very active disease were largely asymptomatic or had very limited function impairment attributable to Paget's disease.

Safety

The improved potency of nitrogen-containing bisphosphonates opens the way to the intravenous administration of small amounts of drug, but needs to be accompanied by a clear demonstration of safety. A number of different issues have been addressed by recent clinical trials. 'Post-dose symptoms' are common after the intravenous administration of nitrogen-containing bisphosphonates and had previously been demonstrated with pamidronate [18]. Subsequent studies showed that this was due to accumulation of isopentyl diphosphate (a precursor of cholesterol in the mevalonate pathway) caused by inhibition of the enzyme farnesyl diphosphate synthase [19]. Isopentyl diphosphate activates γδT cells, which in turn leads to the production of IL-6, TNF-α and IFN-γ, thus producing an acute-phase response. Influenza-like symptoms, myalgia, pyrexia and bone pain are grouped together under the term 'post-dose symptoms' and are particularly common in the first 3 days after intravenous administration of nitrogen-containing bisphosphonates. This occurred in 28.2% of the patients treated with zoledronic acid but was only obvious in 8.1% of patients given risedronate. The symptoms are fairly mild and transient and can often be minimized by the administration of prophylactic paracetamol or ibuprofen. Other symptoms that commonly occur in the first 3 days after the administration of this type of bisphosphonate include fatigue, headache, rigors and nausea; one or more of these adverse events occurred in 53.7% of patients treated with zoledronic acid and 25% of patients treated with risedronate. These latter symptoms appear to be general adverse events that are not particularly restricted to nitrogen-containing bisphosphonates.

Intravenous bisphosphonates are commonly used in the treatment of hypercalcemia associated with malignant disease and there had been concern that they may contribute to the renal impairment often seen in these patients. However, it is well recognized that multiple factors are involved, including the renal effect of hypercalcemia, the treatment for malignant disease

and dehydration due to nausea or vomiting. The trials of Paget's disease only recruited patients with a glomerular filtration rate greater than 30 ml/min, but there was no effect on serum creatinine when values at baseline and at days 9–11 were compared.

Rapid inhibition of bone resorption by intravenous bisphosphonates, with a slower fall in bone formation, may lead to asymptomatic hypocalcemia, which is similar to the 'hungry-bone syndrome' seen after parathyroidectomy for primary hyperparathyroidism. A total of eight patients treated with zoledronic acid developed hypocalcemia, which was asymptomatic in six, while the two with mild symptoms had omitted their calcium/vitamin D supplementation. One patient treated with risedronate had severe symptomatic hypocalcemia, which required hospitalization for intravenous calcium, despite calcium and vitamin D supplementation. In all patients, serum calcium returned to baseline at 6 months. The hypocalcemia was accompanied by mild secondary hyperparathyroidism at 3 months but had almost returned to baseline 3 months later. These changes emphasize the importance of calcium/vitamin D repletion when treating patients with Paget's disease with potent intravenous bisphosphonates; the risk is likely to be greater in those with the most active bone turnover.

Cost–effectiveness/practicalities of management

The ability to maintain control of Paget's disease over a period of years is central to the cost–effectiveness of treatment. Long-term costs are greatly reduced if the need for bisphosphonate re-treatment can be avoided, although there may be small additional savings owing to the requirement for less frequent clinic attendances and biochemical testing. Several cost-effective estimates, projected over a 2-year time period, have been based on the results of the pivotal trial in Paget's disease. These examined direct costs, including bisphosphonate prescriptions, clinic monitoring visits, laboratory testing and radiography, but excluded medication for post-dose symptoms, since patients would buy this from the local pharmacy. Treatment with zoledronic acid involved savings of €243 compared with risedronate [20] and €559 compared with intravenous pamidronate [21], although this latter figure will decrease as the cheaper generic pamidronate becomes more widely available. These estimates may prove to be conservative since the remission rates with zoledronic acid may be better than the preliminary reports suggest [2,3] and may extend beyond 2 years.

Paget's disease is becoming less common [22], and since primary-care experience of the disease will also decrease, it will be treated most effectively by specialist centers who will assess new cases and initiate treatment. However the sustained remission achieved with zoledronic acid will also promote a shift back from secondary to primary care for follow-up and biochemical monitoring.

Conclusion

Zoledronic acid represents a substantial improvement to the treatment of Paget's disease, but only prolonged observation will show whether this is accompanied by a reduced incidence of long-term complications. It is unusual for such an advance to prove cost effective; this is likely to be complimented by a change in the division of care between the primary and secondary sectors.

Expert commentary

The main challenges to effective management of metabolic bone disease with bisphosphonates are the achievement of consistent compliance with drug therapy and the sustained control of bone turnover at the target level. Oral bisphosphonate therapy is demanding for the patient, who has to take the drug while fasting and delay food/medication for at least 30 min. Some patients also experience symptoms of esophagitis, and compliance at 1 year is approximately 50%. The availability of an effective treatment as a single 15-min infusion overcomes these difficulties. It will be interesting to see whether treatment remains the province of secondary care or whether it will move out into general practice.

Other relevant issues include the ability to control symptoms, as well as biochemical markers of bone turnover and the cost–effectiveness of treatment. Very few previous trials in Paget's disease have been able to demonstrate symptomatic benefit, but this is very important for the payers of healthcare. The recent large clinical trial of zoledronic acid recruited on the basis of increased bone turnover rather than symptoms. However, the large size of the study and the substantial fall in bone turnover was accompanied by improvements in QoL, as assessed by the SF-36.

Cost–effectiveness is a major determinant of whether a drug will become first-line treatment. In Paget's disease, the cost of long-term treatment is largely driven by the need to re-treat.

The ability of zoledronic acid to produce sustained control of bone turnover within the therapeutic target range yields high cost–effectiveness. The prolonged remission also facilitates the transfer of long-term management from secondary to primary care. This is a goal of many healthcare systems and will also contribute to cost–effectiveness.

Future perspective

It is probable that we will not see further substantial improvements in potency or skeletal retention of bisphosphonates. The major changes over the next few years will be in the way that treatment is delivered. The ability to give an effective dose of bisphosphonate as a single, short infusion is an advance over prolonged oral therapy, but is limited by the willingness of some sectors of the healthcare system to give intravenous infusions. Paget's disease is much less common than osteoporosis and it would be feasible to treat most patients in this way in secondary care.

Monoclonal antibodies that target the RANKL–osteoprotegerin system have been studied in clinical trials in osteoporosis. Denusomab, a monoclonal antibody targeting RANKL, is given as a 6-monthly subcutaneous injection and will have more general applicability in primary care. Development of more convenient routes of administration that have the advantage of supervision are a good way to combine effective treatment with good compliance. As always, safety will be an issue, but preliminary trials in osteoporosis are reassuring in this respect. There are no current trials of this approach in Paget's disease.

Executive summary

- Zoledronic acid is a potent bisphosphonate with prolonged skeletal retention.
- A single 5-mg infusion restores normal bone turnover in 90% of patients.
- This is accompanied by an improvement in symptoms/quality of life.
- Bone turnover remains within the reference range for several years.
- Potency and prolonged remission contribute to cost–effectiveness.
- Zoledronic acid may become the first-choice drug for Paget's disease.

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