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ORIGINAL ARTICLE

Re-treatment of relapsed Paget's disease of bone with zoledronic acid: results from an open-label study

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Six patients from the phase 3 trials of zoledronic acid in Paget's disease, who had received zoledronic acid initially and had subsequently relapsed, were entered into an open re-treatment study. Following re-treatment, each patient reached similar absolute nadirs of serum alkaline phosphatase to those recorded after their first dose. No significant adverse events were reported. It is concluded that, while re-treatment of Paget's disease with zoledronic acid is rarely needed, it is safe and effective, with no evidence of treatment resistance based on this small cohort.

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Introduction

Zoledronic acid has revolutionized the management of Paget's disease, producing therapeutic responses in 96% of patients and normalization of serum total alkaline phosphatase (ALP) in 89% of patients 6 months after a single 5 mg infusion.[1] These responses are sustained in the great majority of patients. In those showing a response at 6 months, this is still present after 6.5 years follow-up in 87% of patients.[2] As a result of this high level of sustained efficacy, there is little experience with re-treatment of Paget's disease using zoledronic acid. However, the above figures indicate that this will sometimes be necessary, so it is important to document the efficacy and safety of this. The present paper describes re-treatment in six patients from the phase 3 trials, for whom this was appropriate.

Results

Of 169 zoledronic acid-treated patients in the core studies, 152 entered the post-trial observation period. Of these, six met the criteria for inclusion in this re-treatment study and were at sites involved in this part of the program.

The mean age of these patients was 75 years. Demographic and baseline characteristics of the enrolled patients are shown in **Table 1**. The mean time from the initial treatment to re-treatment was 6.5 years and the mean relapse-free period, defined as the period from the initial therapeutic response to the re-treatment, was 6.4 (range 6.0–7.7) years. All patients had elevated ALP, the mean value being 200 U l^{-1}. Two patients had another indication for re-treatment (bone scan activity in patient 1 and pain in patient 3).

Efficacy. The individual patient ALP data from the time of initiation of the core studies are shown in **Figure 1**. Three months after re-treatment all had normal levels, which were maintained at 6 months, with the exception of patient 4 whose ALP value at 6 months was just above normal (117 U l^{-1}), probably not a significant change from the 3-month value of 104 U l^{-1}. All patients reached approximately the same nadir in ALP after the second treatment as had been reached after the first (within 12 U l^{-1} in five; patient 4 had reached 76 U l^{-1} after the first infusion of zoledronic acid but only reached 104 after the second). The mean decreases in ALP were 53% at month 3 and 50% at month 6 (**Figure 2**).

Patient 2 had minimal elevation of ALP above the previous plateau before re-treatment, and minimal response to the second dose of zoledronic acid. Serum calcium at the time of re-treatment was 2.74 nmol/l, although parathyroid hormone and serum phosphate were normal. Thus, it is possible that the small increase in ALP at this time reflected some bone pathology other than Paget's disease.

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Table 1 Baseline demographic and disease characteristics of the study population

Variable	
Male, *n*	4
Caucasian, *n*	5
Age (years)	75 ± 6 (66–85)
Weight (kg)	67.8 ± 10.4 (47.8–76.0)
BMI (kg m^{-2})	25.4 ± 4.0 (17.8–29.7)
Serum calcium (mmol l^{-1})	2.46 ± 0.17 (2.23–2.74)
Creatinine (μmol l^{-1})	84 ± 31 (51–140)
Creatinine clearance (ml min^{-1})	67 ± 23 (33–103)
ALP (U l^{-1})	200 ± 60 (117–293)
Relapse-free period (months)	77 ± 11 (60–92)

Abbreviations: ALP, serum total alkaline phosphatase; BMI, body mass index. Data are mean ± s.d. (minimum–maximum).

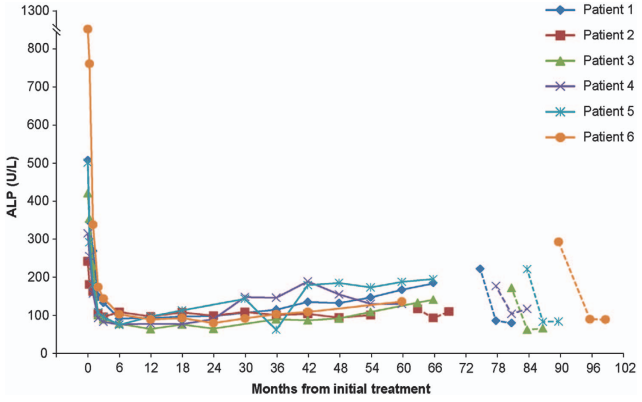

Figure 1 Individual patient data for serum total ALP from the initiation of the core studies. All subjects received an infusion of zoledronic acid 5 mg at month 0, and again at the beginning of the re-treatment period. Data from the 6-month core study and the subsequent open observation period are shown with solid lines. Data for the 6-month re-treatment period are shown with broken lines. The re-treatment data for patient 2 are shown between months 63 and 69, overlapping the post-trial observation period for the other patients. The reference range for ALP is 31–110 U l^{-1}.

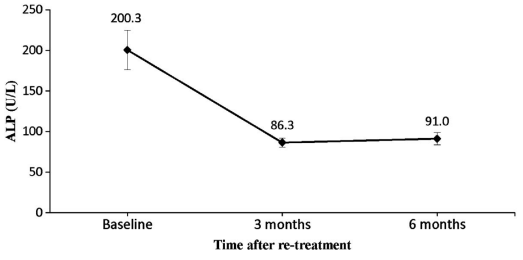

Figure 2 Effect of re-treatment with zoledronic acid on serum total ALP at months 3 and 6. Data are shown as mean ± s.e. ($n = 6$).

Safety. No serious adverse events or deaths were reported during the study. One patient developed mild influenza >3 weeks after re-treatment, which was not thought to be treatment related.

Discussion

The small number of patients needing to enter a re-treatment protocol after 6–8 years of follow-up from a single infusion of zoledronic acid provides evidence of the efficacy and longevity of this treatment. Those patients coming to re-treatment all did so with ALP values well below the levels they had before treatment with zoledronic acid. Following re-treatment, they again reached the same absolute nadirs previously recorded, indicating that there was no development of resistance to this therapy. Obviously, the percent decrease in ALP following re-treatment was much less than initially, because the basal values were much lower, but it is the absolute levels of ALP that are indicative of the disease activity.

Reports of re-treatment of Paget's disease with bisphosphonates are rare. The responses found in this study are very similar to initial reports of re-treatment of Paget's disease with oral pamidronate, where the initial nadirs were recapitulated after a second course of bisphosphonate,[3] and after intravenous clodronate.[4] Subsequently, it has been reported that the same nadir was not reached by patients requiring a third course of pamidronate, suggesting that some form of resistance might develop.[5] In contrast, it appears that re-treatment with etidronate is less effective than administration of this drug to treatment-naive patients,[6] but this is a much less potent agent that has a different molecular target in bone.

Re-treatment produced no unexpected side-effects. As zoledronic acid is administered as monthly infusions in oncology patients and annual infusions in those with osteoporosis, there is already extensive safety data regarding re-treatment, and this small patient sample merely serves to indicate that the pagetic patients hold no surprises in this regard. The most common side-effect of zoledronic acid is the acute phase response, which is much less frequent, and milder when it does occur, with the second and subsequent doses.[7]

An important question raised by these data is when is it necessary to re-administer zoledronic acid to patients with Paget's disease? Many experienced physicians have liberalized their policies with respect to initial treatment of Paget's disease because zoledronic acid produces such a high rate of sustained biochemical remission. Thus, treatment is often the cheapest option because of the savings in costs of follow-up. Treatment with zoledronic acid is associated with improved quality of life,[1,2] and bisphosphonate treatment has been shown to be associated with restoration of normal bone histology and healing of radiographic lytic lesions.[8] From our knowledge of the natural history of radiologic lytic lesions,[9] this would be expected to reduce pagetic deformity and the clinical sequelae that follow from it, such as osteoarthritis, pain and fracture. The widespread clinical experience of the last 20 years, since potent bisphosphonates became available, is in accord with this. When patients show biochemical relapse, re-treatment may again be the most economical option because it reduces the frequency of follow-up assessments. However, there should also be a critical consideration of what the adverse clinical consequences of the ongoing low levels of pagetic activity are likely to be. This will depend on the clinical context. For instance, in a patient who has experienced paraplegia as a consequence of Paget's disease, most experts would continue to manage this vigorously, treating any evidence of disease activity, even if this was only manifest on bone scintigraphy and not apparent in circulating levels of bone markers. Similarly, the presence of lytic disease in long bones (which carries the future risk of deformity and fracture), juxta-articular disease (with the risk of osteoarthritis) or active disease in the temporal bone (with

the risk of progressive hearing impairment) should all be managed vigorously. In contrast, in an asymptomatic patient who is not at risk of complications in the foreseeable future, it may be perfectly reasonable to leave low levels of disease activity without specific intervention. This approach is consistent with guidelines that were framed in the pre-zoledronate era.[10,11]

In summary, the present small case series demonstrates the efficacy and safety of re-treatment of Paget's disease with zoledronic acid, and raises the important issue of when such intervention is likely to be necessary.

Materials and Methods

Study design. This study was a 6-month, open-label, non-randomized, multicenter, single-arm, phase IV trial in patients with relapsed Paget's disease of bone, who had previously responded to a single intravenous infusion of zoledronic acid in the core registration trials, and were then followed in an extended observation period. A therapeutic responder during the core study was defined as a patient who had $\geqslant 75\%$ reduction from baseline in ALP excess (the difference between measured level and midpoint of normal range) or an ALP within the normal range at 6 months. During the post-trial observation period, patients who met the criteria for disease relapse could be enrolled in the present re-treatment study. Criteria for relapse were total ALP level that was above the upper limit of normal, or radiographic, scintigraphic or clinical evidence (for example, increasing pagetic pain) of relapse.

Exclusion criteria were use of bisphosphonate or calcitonin within the previous 12 months, hypersensitivity to bisphosphonates, creatinine clearance $<35\,\mathrm{ml\,min^{-1}}$, serum calcium $<2.07\,\mathrm{mmol\,l^{-1}}$, pregnancy, lactation, active iritis, uveitis or episcleritis, primary hyperparathyroidism, hyperthyroidism, hypoparathyroidism, hypothyroidism or malignancy within 12 months before study initiation.

Re-treatment consisted of zoledronic acid 5 mg in 100 ml water by intravenous infusion over at least 15 min. All patients received daily vitamin D 800 IU and calcium supplementation (1500 mg in divided doses) starting at least 5 days before re-treatment and for 2 weeks after zoledronic acid infusion, to reduce the risk of hypocalcaemia.

ALP levels were determined by spectrophotometry (Roche Modular Analyzer, Roche Diagnostics Corporation, Indianapolis, IN, USA)[2] at baseline, and at 3 and 6 months after zoledronic acid re-infusion.

Written informed consent was obtained from each patient. The study was approved by the appropriate institutional review board. The study was conducted according to the ethical principles of the Declaration of Helsinki and is registered with ClinicalTrials.gov with identifier NCT00740129.

Conflict of Interest

IRR has acted as a consultant for Novartis. GS, OA-F and RPA are Novartis employees. The remaining authors declare no conflict of interest.

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