Libraries and Learning Services

University of Auckland Research Repository, ResearchSpace

Version

This is the Accepted Manuscript version. This version is defined in the NISO recommended practice RP-8-2008 http://www.niso.org/publications/rp/

Suggested Reference

Cundy, T., Maslowski, K., Grey, A., & Reid, I. R. (2017). Durability of Response to Zoledronate Treatment and Competing Mortality in Paget's Disease of Bone. *Journal of Bone and Mineral Research*, *32*(4), 753-756. doi:10.1002/jbmr.3029

Copyright

Items in ResearchSpace are protected by copyright, with all rights reserved, unless otherwise indicated. Previously published items are made available in accordance with the copyright policy of the publisher.

This is the peer reviewed version of the article above which has been published in final form at 10.1002/jbmr.3029

This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for self-archiving.

For more information, see General copyright, Publisher copyright, SHERPA/RoMEO.

Accepted Preprint

Original Article

Durability of response to zoledronate treatment and competing mortality in Paget's disease of bone[†]

Tim Cundy*, Katherine Maslowski, Andrew Grey, Ian R Reid

Department of Medicine, Faculty of Medical & Health Science, University of Auckland and Bone Clinic, Endocrinology, Greenlane Clinical Centre, Auckland District Health Board, Auckland, New Zealand.

[*]**Corresponding Author:** Tim Cundy, e-mail: t.cundy@auckland.ac.nz

[†]This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/jbmr.3029]

Initial Date Submitted July 5, 2016; Date Revision Submitted September 29, 2016; Date Final Disposition Set October 30, 2016

Journal of Bone and Mineral Research

This article is protected by copyright. All rights reserved

DOI 10.1002/jbmr.3029

This article is protected by copyright. All rights reserved

Accepted Preprint

Abstract

There has been a marked secular trend in recent decades toward patients with Paget's disease presenting at a greater age and having less extensive skeletal involvement. Over a similar time frame more potent bisphosphonates with a long duration of effect have been developed, raising the prospect of many patients needing only once in a lifetime treatment. We studied a cohort of 107 patients who had been treated with intravenous zoledronate for the first time at a mean age of 76 years. Sequential measurements of the bone turnover marker procollagen-1 NT-peptide (P1NP) were made for up to 10 years. By 9 years, 64% showed some loss of zoledronate effect (defined as a doubling of P1NP from the nadir value after treatment), but only 14% had a biochemical relapse (defined as a P1NP value >80 ug/L). The mortality rate was substantially greater than the relapse rate – by 10 years more than half the cohort had died (P<0.0001). We conclude that for the majority of older people with Paget's disease a single intravenous infusion of zoledronate will provide disease suppression for the remainder of their lives. This article is protected by copyright. All rights reserved

This article is protected by copyright. All rights reserved

Accepted Preprint

Introduction

Paget's disease of bone (PDB) is a focal skeletal disorder of unknown cause characterized by high rates of resorption and formation in affected bones. The clinical consequences include bone pain, fracture, deformity, secondary osteoathritis and, if the skull is involved, deafness. Although its efficacy in preventing the long-term complications has not been proven, bisphosphonate therapy is highly effective at reducing the abnormally high rate of turnover in pagetic bone and reducing bone pain. However, the response with agents such as pamidronate and risedronate is often of relatively short duration, with relapse after therapy, indicated by rising levels of bone turnover markers, being common [1,2].

In recent years bisphosphonates of progressively greater potency that can produce long-lasting remissions in PDB have been introduced into clinical practice. In a large randomized clinical trial, the most potent bisphosphonate tested to date, zoledronate (zoledronic acid), induced a therapeutic response in 97.5% of patients within 6 months. A therapeutic response was defined as normalization of the total alkaline phosphatase (tALP) level or a reduction of at least 75% in the tALP excess - that is the difference from the midpoint of the reference range [3]. In a follow up study, relapse, defined as a rise in tALP to within 20% of its pre-treatment value, occurred in less than 1% of subjects up to 6½ years after a single infusion, though loss of therapeutic response (defined as above), occurred in 12.5% [2].

The subjects in this clinical trial were in some ways atypical of patients with PDB now seen in clinical practice, as almost all the participants had tALP values at least twice the upper limit of normal, indicating moderate or severe disease. In recent decades there has been a marked secular change in the clinical presentation of PDB and compared to 40 years ago patients are significantly older at diagnosis and have less severe disease (meaning fewer bones involved with PDB) [4]. It is now common for patients with disease of limited extent to have tALP values that are not elevated above the normal range [5]. The combination of milder disease occurring in older patients on the one hand, coupled with the use of more potent bisphosphonates with a long duration of effect on the other, raises the prospect of many patients needing only once in a lifetime treatment, or even 'cure' of the disease [6].

In this study we report the follow-up for 6 to 10 years of a cohort of PDB patients who were treated with a single intravenous zoledronate infusion between 2005 and 2009, examining both mortality and biochemical evidence suggesting re-activation of the disease. To assess

This article is protected by copyright. All rights reserved

the latter we have used the sensitive, treatment-responsive and bone-specific turnover marker procollagen-1 NT-peptide [7].

Subjects and Methods

We studied 107 patients [44 women, 63 men] with PDB who received treatment between August 2005 (when we first began using zoledronate) and December 2009. Data as of January 2016 was used in this analysis, meaning that a potential 6-10 years' follow up was available in all subjects. Zoledronate was given as a single intravenous infusion. A 4mg dose (*Zometa,* Novartis) was used up to May 2008 (71 subjects) and, because of a brand change, a 5mg dose (*Aclasta,* Novartis) was used from June 2008 (36 subjects).

49 subjects (46%) had previously been treated with other bisphosphonates, given either orally (etidronate or alendronate) or intravenously (clodronate, pamidronate or ibandronate). The extent of involvement with PDB was estimated from skeletal scintigraphy, using the method of Coutris et al [8]. Four patients with familial PDB were known to have mutations in exon 8 of the gene encoding sequestosome 1.

We chose to use the bone-specific turnover marker plasma procollagen-1 NT-peptide (P1NP) because of its advantages over tALP: P1NP is usually elevated in people with disease of limited extent, responds rapidly after treatment and rises early in the course of relapse [7,9]. P1NP was measured at the time of clinic visits, and not batched for later analysis. The assay used an electrochemiluminescence method (E170, Roche Diagnostics, Mannheim, Germany). The inter-assay coefficient of variation was 2-5%.

Sequential measurements of P1NP were made at intervals of 6-12 months during follow up. We noted the nadir value after treatment and its timing, and looked at two indicators of durability of response: the time after treatment at which P1NP levels first exceeded twice the nadir value, and 'biochemical relapse' - the time at which P1NP first exceeded 80 ug/L - the upper limit of normal in men. In some patients a relatively acute rise and fall in P1NP was noted following fractures or joint replacement surgery. These episodes were excluded from the analyses. Deaths were confirmed from the medical record.

Statistical analysis

Data are expressed as the mean with standard deviation, or median and range. Kaplan-Meier survival analysis was used to describe durability of response to zoledronate treatment

This article is protected by copyright. All rights reserved

Accepted Preprint

and all-cause mortality. All calculations were made using the GraphPad Prism v5.00 statistical program.

Results

At the time of the zoledronate infusion the mean age of the 107 subjects was 76 [SD 10] years, and the median involvement on skeletal scintigraphy was 10% Before treatment the median P1NP concentration was 182 ug/L and 75 patients had P1NP values >80 ug/L. The median nadir P1NP concentration was 23 ug/L (Table). Nadir values were observed a median 24 months after treatment (range 6 to 90 months). The mean duration of follow up was 7 years.

Ten patients died without having any post-treatment P1NP measurements made. These were aged 75-97 years [median 88 yrs] and mainly cared for in facilities for the elderly. The time of death in this group was 1-91 months after receiving zoledronate; only 2 of the 10 died >6 yrs after zoledronate.

We took the time after treatment at which P1NP levels first exceeded twice the nadir value as indicating waning of the effect of the bisphosphonate. By this criterion 9% showed loss of effect by 3 years, 34% by 6 years and 64% by 9 years (Figure 1A). There was no significant difference in the occurrence of this end point between patients who had or had not been treated previously with bisphosphonates (p=0.730); between those receiving the 4 and 5mg doses (p=0.266); between men and women (p=0.890); between those with pre-treatment P1NP values above or below the median (p=0.077); between those with nadir P1NP values above or below the median (p=0.417); or between those with skeletal involvement above or below the median (p=0.410).

Using the more stringent criterion of biochemical relapse (P1NP >80 ug/L), no subjects had relapsed by 3 years, 5% by 6 years and 11% by 9 years (Figure 1A). Restricting this analysis to the 75 subjects whose P1NP was >80 ug/L pre-treatment, 6% had relapsed by 6 years and 14% by 9 years (Figure 1B). The P1NP level at the time of relapse was 2.1 – 6.4 times (median 3.5) the nadir value. In these patients the median tALP was 178 u/L (range 96-477) before treatment; 65 u/L (range 46-92) at the nadir and 104 u/L (range 66-277) at the time of relapse (as judged by P1NP >80 ug/L). The tALP level at the time of relapse was 1.1 – 3.0 times (median 1.7) the nadir value.

This article is protected by copyright. All rights reserved

Accepted Preprint

The mortality rate was high. Three years after treatment 6% had died; after 6 years, 23%; and after 9 years, 39%. More than half the patients had died within 10 years of treatment. The chances of dying during follow up were statistically much greater than that of a biochemical relapse (P<0.0001, Figure 1B). We did not have access to death certificates to determine cause of death.

Discussion

While the data we present is observational it does convey a number of important messages. First, the patients whose progress after treatment we followed were typical of modern day practice, with a largely elderly population with disease of limited extent, as assessed by skeletal scintigraphy. In contrast to the subjects in the RCT of zoledronate treatment of PDB [2,3] the mean pre-treatment P1NP measurement in our population was lower (225 vs 438 ug/L), and the mean age was greater (76 vs 70 years). Thus the patients in this study more closely resembled those in the PRISM trial which compared intensive and symptomatic-only bisphosphonate treatment. A high proportion of participants in that trial (36%) had only one bone involved with PDB, and the mean age at entry was 74 years [5].

Second, our period of observation of up to 10 years meant we could observe the long-term effects of zoledronate on bone turnover, beyond the 6½ year point reported in the RCT follow-up study[2]. We found biochemical evidence of waning of the bisphosphonate effect over time - with 64% having a doubling of P1NP from the nadir value by 9 years, but within the same period only 11% of subjects had a biochemical relapse, as defined by a P1NP level rising >80 ug/L. It is possible that relapse could have occurred and been missed in some of the 10 patients who died without follow-up P1NP measurements, but eight of these died <6 years after receiving zoledronate, so this is would not have altered the results substantially.

Some of the increase in PINP above the nadir may represent a waning of the zoledronate effect in non-pagetic bone, so this measure may overestimate the loss of therapeutic effect. The low relapse rate 9 years after treatment emphasises the very prolonged duration of action of zoledronate – findings that replicate those observed in post-menopausal women and men with HIV infection [10,11].

Third, we have documented that over the period of follow-up there was a substantial mortality rate. This was not surprising given that the average age of the population was high and the majority were men. The mortality rate at 10 years was nearly four times higher than

This article is protected by copyright. All rights reserved

Accepted Preprint

the biochemical relapse rate. So while the biochemical data outlined above suggests that zoledronate is unlikely to produce a *biological* cure of PDB by completely preventing relapse, it does indicate that a once in a lifetime dose has a high chance of producing an *effective* cure. In the elderly with disease of limited extent, competing mortality means many patients die before relapse becomes evident. Understanding this could spare such patients unnecessarily frequent follow up.

Limitations to this study include its observational nature and the fact that almost half the subjects had previously been treated with bisphosphonates, and a third had pre-treatment P1NP values within the normal range. Our definition of biochemical relapse – a P1NP value >80 ug/L - the upper limit of the normal range in men – was an arbitrary one (as indeed are all definitions of relapse). The quoted upper limit of normal in postmenopausal women is higher than this (>115 ug/L) but adding this criterion would have resulted in only one woman, whose P1NP value reached 96 ug/L, being reclassified from relapse to non-relapse. The zoledronate dose was also changed from 4 to 5mg during the study. However, none of these factors appeared to impact on the time to first offset of action of zoledronate. Most previous studies of relapse and remission in PDB have used tALP as the primary bone marker, rather than P1NP. We chose to use this bone-specific turnover marker because of its advantages over tALP which also has non-osseous sources and may be in the normal range in people with disease of limited extent [7,9].

Accepted Preprint

This article is protected by copyright. All rights reserved

Accepted Preprint

References

1. Miller PD, Brown JP, Siris ES, Hoseyni MS, Axelrod DW, Bekker PJ. A randomized, double-blind comparison of risedronate and etidronate in the treatment of Paget's disease of bone. Am J Med. 1999; 106:513-20.

2. Reid IR, Miller P, Lyles K, Fraser W, Brown JP, Saidi Y, Mesenbrink P, Su G, Pak J, Zelenakas K, Luchi M, Richardson P, Hosking D. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. New Engl J Med 2005; 353: 898–908.

3. Reid IR, Lyles K, Su G, Brown JP, Walsh JP, Del Pino-Montes J, Miller PD, Fraser WD, Cafoncelli S, Bucci-Rechtweg C, Hosking DJ. A single infusion of zoledronic acid produces sustained remissions in Paget disease: data to 6.5 years. J Bone Miner Res 2011; 26: 2261–70.

4. Cundy HR, Gamble G, Wattie D, Rutland M, Cundy T. Paget's disease of bone in New Zealand: continued decline in disease severity. Calcif Tissue Inter 2004; 75: 358-64.

5. Langston AL, Campbell MK, Fraser WD, MacLennan GS, Selby PL, Ralston SH; PRISM Trial Group. Randomized trial of intensive bisphosphonate treatment versus symptomatic management in Paget's disease of bone. J Bone Miner Res 2010; 25:20-31.

6. Reid IR. Treatment of Paget's disease of bone. In: Advances in Pathobiology and Management of Paget's Disease of Bone. Ed: SV. Reddy. Academic Press 2016: pp 119-36.

7. Reid IR, Davidson JS, Wattie D, Wu F, Lucas J, Gamble GD, Rutland MD, Cundy T. Comparative responses of bone turnover markers to bisphosphonate therapy in Paget's disease of bone. Bone 2004; 35: 224-230.

8. Coutris G, Cayla J, Rondier J, Talbot JN, Bonvarlet JP, Milhaud G. Analyse des perturbations des voies principales du metabolisme calcique dans la maladie de Paget: effects de l'administration de calcitonine. Rev Rhumat Malad Osteo-Artic 1975; 42: 759–767.

9. Cundy T, Reid IR. Paget's disease of bone. Clin Biochem. 2012; 45(1-2): 43-8.

10. Grey A, Bolland MJ, Horne A, Wattie D, House M, Gamble G, Reid IR. Five years of anti-resorptive activity after a single dose of zoledronate--results from a randomized double-blind placebo-controlled trial. Bone 2012; 50:1389-93.

11. Bolland MJ, Grey A, Horne AM, Briggs SE, Thomas MG, Ellis-Pegler RB, Gamble GD, Reid IR. Effects of intravenous zoledronate on bone turnover and bone density persist for at least five years in HIV-infected men. J Clin Endocrinol Metab 2012; 97:1922-8.

This article is protected by copyright. All rights reserved

Accepted Preprint

Table

	Mean or Median*	Range
Age (years)	76	47-97
Proportion of skeleton involved (%)	10*	1-41
Pre-treatment P1NP (ug/L)	182*	18-860
Nadir P1NP (ug/L)	23*	7-64

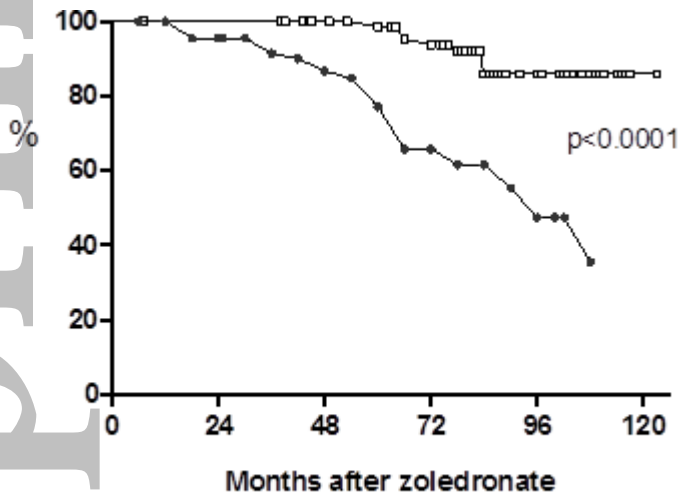
Legend to Figure

Figure 1 A. Proportions of subjects who did not have a doubling of P1NP from its nadir value (dark symbols; 97 subjects) or biochemical relapse (open symbols) in relation to time after the zoledronate infusion. Biochemical relapse was defined as a P1NP value rising after the post-treatment nadir to >80 ug/L (in this analysis, only the 75 subjects whose pre-treatment P1NP was >80 ug/L were included).

B. Proportions of subjects who were alive (dark symbols; 107 subjects) or who did not have biochemical relapse (open symbols) in relation to time after the zoledronate infusion. Biochemical relapse was defined as a P1NP value rising after the post-treatment nadir to >80 ug/L (in this analysis, all 97 subjects who had P1NP measurements made after treatment were included).

This article is protected by copyright. All rights reserved

Accepted Preprint



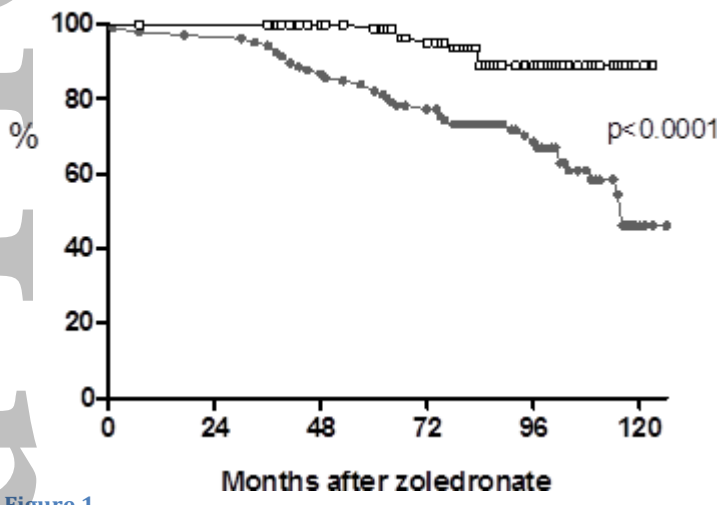


Figure 1

This article is protected by copyright. All rights reserved