ELSEVIER

Bone 42 (2008) 1219–1225

BONE

www.elsevier.com/locate/bone

Treatment of Paget's disease of bone: A survey of clinical practice in Australia

J.P. Walsh [a,b,*], R. Attewell [c], B.G.A. Stuckey [a,b], M.J. Hooper [d,e], J.D. Wark [f], S. Fletcher [g], V. Ferrari [g], J.A. Eisman [h]

[a] *Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia*
[b] *School of Medicine and Pharmacology, University of Western Australia, Crawley, WA 6009, Australia*
[c] *Covance Pty Ltd, Braddon, ACT 2612, Australia*
[d] *Sydney South West Area Health Service, Sydney, Australia*
[e] *University of Sydney, Sydney, Australia*
[f] *Department of Medicine, University of Melbourne, Bone and Mineral Service, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia*
[g] *Novartis Pharmaceuticals Australia Pty Ltd, North Ryde, NSW 2113, Australia*
[h] *Bone and Mineral Research Program, Garvan Institute of Medical Research, Sydney, NSW, Australia*

Received 23 November 2007; revised 14 January 2008; accepted 31 January 2008
Available online 16 February 2008

Abstract

Consensus guidelines for the treatment of Paget's disease of bone have been published, but it is not known how closely these reflect clinical practice. We conducted a multi-centre, stratified, retrospective review of case notes of 531 subjects treated for Paget's disease of bone between 2000 and 2005 in 29 Australian centres. The subjects received 1072 courses of bisphosphonate treatment (pamidronate 363, alendronate 324, risedronate 208, tiludronate 103, zoledronic acid 69, and etidronate 5). The most recent treatment received was oral therapy in 57% of patients (alendronate 29%, risedronate 24%, and tiludronate 4%) and intravenous in 43% (pamidronate 33%, and zoledronic acid 10%). For oral bisphosphonates, the percentages of courses which were at the recommended dosage and duration were: alendronate 33%, risedronate 60% and tiludronate 29%. Pamidronate was administered in a wide range of dosing schedules, most commonly 60 mg every 3 months (18%), 6 months (17%) or annually (12%), whereas zoledronic acid was mainly given as a 4 mg infusion (98%) as a single dose (52%) or annually (19%). Most clinicians reported taking into account symptoms, plasma alkaline phosphatase activity and anatomical location of disease in determining the need for treatment. Patient preference, intolerance of oral therapy and compliance were ranked highest in determining the choice between oral and intravenous therapy. We conclude that oral and intravenous bisphosphonate dosing regimens are both commonly used to treat Paget's disease of bone in Australia. Only a minority of courses of oral bisphosphonate treatment are at the recommended dosage and duration, and there is a lack of consensus on regimens for intravenous treatment.

Keywords: Paget's disease of bone; Bisphosphonate; Clinical guidelines; Clinical audit; Patient compliance

Introduction

Paget's disease of bone is a chronic disorder characterised by foci of excessive osteoclastic bone resorption accompanied by increased osteoblastic activity [1–5]. This results in the formation of structurally abnormal, expanded bone with a propensity to deformity, fracture and very rarely malignant transformation. Although associated with a range of clinical complications, the disease is often asymptomatic, and the benefits of treatment in asymptomatic individuals are uncertain.

Two recent sets of consensus guidelines for the management of Paget's disease have been published, the first commissioned by the American Society for Bone and Mineral Research (ASBMR) [1] and the second by the Bone and Tooth Society of Great Britain and the National Association for the Relief of Paget's Disease [2]. Both documents note the uncertainties surrounding the indications for pharmacological treatment (and re-treatment) and the lack of evidence that treatment prevents

* Corresponding author. Department of Endocrinology and Diabetes, Sir Charles Gairdner Hospital, Nedlands, WA 6009, Australia. Fax: +61 8 9346 3221.
E-mail address: john.walsh@health.wa.gov.au (J.P. Walsh).

8756-3282/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.bone.2008.01.024

long-term complications of the disease. There is, however, general consensus in the literature that potent nitrogen-containing bisphosphonates such as alendronate, pamidronate, risedronate and zoledronic acid are currently the treatments of choice, and are considered to be more effective than calcitonin, etidronate or tiludronate [1–6].

Bisphosphonate treatment for Paget's disease can be administered orally or intravenously, and the factors that affect physicians' choice of drug and route of administration are largely unknown. For oral bisphosphonates, the approved treatment schedules are based on key clinical trials [7–9], but for pamidronate a wide range of treatment regimens has been used [10–22], and there is no consensus in the literature on the optimal dosage, frequency of administration or duration of treatment [1–6]. With regard to choice of drug, there are only three head-to-head, randomised controlled trials comparing potent bisphosphonates for the treatment of Paget's disease. In the first, oral alendronate had similar efficacy to intravenous pamidronate in patients with previously untreated disease, whereas alendronate was more effective in patients previously treated with pamidronate [21]. More recently, a single dose of zoledronic acid 5 mg given intravenously was reported to be more effective than a two month course of oral risedronate [23,24], and a 4 mg infusion of zoledronic acid dose was more effective than intravenous pamidronate given as two 30 mg doses [22].

Because of these uncertainties, and the lack of any published data as to how far the consensus guidelines reflect clinical practice, we carried out a multi-centre survey of the treatment of Paget's disease of bone in Australia.

Materials and methods

The study was a multi-centre, stratified, retrospective review of treatment records. Eligible patients had been treated for Paget's disease of bone at least once in the period from 2000 to 2005 in a hospital setting or in specialist private practice. In Australia, patients with Paget's disease initially consult a general (family medicine) practitioner, and are then usually referred to a public hospital outpatient clinic or to a specialist in private practice. The following drugs are approved by the Australian Therapeutic Goods Administration for the treatment of Paget's disease of bone: salmon calcitonin, etidronate, tiludronate, pamidronate disodium, alendronate sodium and risedronate sodium. Zoledronic acid is not yet approved in Australia for the treatment of Paget's disease, but is approved (as a 4 mg infusion) for malignant bone disease. The Australian Pharmaceutical Benefits Schedule subsidises the cost of approved medications for patients treated in private practice for "symptomatic Paget's disease of bone" (not otherwise defined). Treatment for asymptomatic patients is not subsidised through this scheme, but is available through some public hospitals or on private prescription.

Clinicians specialising in bone and mineral disorders at major public hospitals in Sydney, Melbourne and Perth were approached directly to participate in the study. To identify other potential sites for the survey, a questionnaire was mailed to 550 endocrinologists and rheumatologists across Australia in June 2005, asking for the number of patients with Paget's disease that they treated and inviting participation in the study. Responses were received from 95 clinicians, of whom 27 participated in the study, which took place from August to December 2005.

Participating sites were ranked in four strata according to the number of eligible patients, and a random sample of patients was selected for case note review. In sites with less than 20 eligible patients, the records of 5 were reviewed; in those with 20–49 eligible, 10 were reviewed; in those with 50–99, 20 were reviewed and in those with more than 100 subjects, 40 were reviewed. For each subject, the following information was requested: year of birth, gender, year of diagnosis, serum alkaline phosphatase (ALP) at diagnosis, bones affected by Paget's disease and the clinical setting in which the patient was treated (hospital-based public patient, hospital-based private practice or community-based private practice). For each treatment course administered after January 2000, the date of starting and finishing treatment; drug, dose and frequency of administration; indication for treatment (from a checklist of biochemistry, X-ray, bone scan, symptoms, other) and reason for stopping treatment were recorded. For oral bisphosphonates, a treatment course was defined as a continuous period of treatment with a single therapy at a specific dose and frequency. For intravenous bisphosphonates, a course was defined as one or more infusions of the same drug without intervening treatment with another drug, and the duration defined as the time in months from the first infusion until the last infusion or the date of case note review (for ongoing treatments). Arbitrarily, if 12 months or more elapsed between two infusions, the second infusion was regarded as the start of new course. Participating clinicians were also asked to complete a two page questionnaire examining their usual treatment practice for Paget's disease of bone. The questionnaires used in the study are available on the journal website.

The primary outcome measure was the number and percentage of patients receiving each treatment. Because of the likelihood that patients received different treatments during the study period and had periods without treatment, this was defined as the most recent treatment received. Secondary outcome measures included dosage and duration of treatment for each drug, criteria for initiating and stopping treatment and patient characteristics associated with use of intravenous versus oral treatment. We calculated that a sample size of 500 patients would provide adequate precision for the primary outcome measure, expecting that the 95% confidence intervals for the percentage of patients treated with any particular therapy would be at maximum ±6%, adjusting for the clustering of patients per site with a hypothesized design effect of 2 (or intra-cluster correlation of 0.09).

Completed survey forms were analysed centrally. No data query resolution was undertaken, but feedback was given to the sites after the completion of the first survey form to ensure accurate and uniform completion across the study centres. Descriptive statistics were computed for outcome

Table 1
Characteristics of the 531 subjects audited

Male	282	54%
Age at audit, year, mean (SD)	75	(10)
Age at diagnosis, year, mean (SD)	65	(12)
ALP at diagnosis (IU/L) [a]		
<100	34	8%
100–299	228	54%
300–499	80	19%
500–999	54	13%
≥1000	27	6%
Number of bone sites affected [b]		
1	201	39%
2	122	23%
3 or more	199	38%
Bones affected		
Pelvis/sacrum	338	65%
Spine	197	38%
Skull	163	31%
Femur	200	38%
Tibia	200	38%
Other	191	37%
Treatment setting		
Community-based private patient	265	50%
Hospital-based public patient	162	31%
Hospital-based private patient	101	19%

Data are shown as number of subjects and percentage except where indicated.
[a] Available for 423 subjects (80% of sample).
[b] From a checklist of pelvis/sacrum, spine, skull, femur, tibia or other. Note that pelvis/sacrum and spine were each counted as a single site.

Table 2
Treatments administered for Paget's disease in 531 subjects between 2000 and 2005

	N	%
Number of treatment courses per patient		
1	229	43%
2	159	30%
3	86	16%
4 or more	57	11%
Number of subjects receiving:		
Oral treatment only	267	50%
Intravenous treatment only	170	32%
Both oral and intravenous treatment	94	18%
Number of subjects receiving each treatment during study period		
Pamidronate	240	45%
Alendronate	205	39%
Risedronate	147	28%
Zoledronic acid	59	11%
Tiludronate	59	11%
Etidronate	3	1%
Most recent treatment (number of patients)		
Pamidronate	173	33%
Alendronate	153	29%
Risedronate	125	24%
Zoledronic acid	54	10%
Tiludronate	23	4%
Other	3	1%

Note that the total number of subjects receiving each treatment exceeds 531 because some subjects received two or more drugs during the study period.

measures and differences between groups compared by chi-square testing. Significance was set at $P<0.05$.

Approval for the study was granted by the Human Research Ethics Committees of each participating hospital and by the Bellberry Ethics Committee, Ashford, South Australia for conducting the study in private practices. Individual patient consent was not sought, since patient data were extracted by study site staff who already had access to patient records, and all data were deidentified prior to analysis.

Results

Demographics and choice of treatment

The records of 535 subjects with Paget's disease of bone managed by 27 clinicians (18 endocrinologists, 8 rheumatologists and 1 geriatrician) were reviewed. Two clinicians each included patients from two separate centres, giving a total of 29 sites in the study. Four patients were excluded because they had not received drug therapy in the observation period. The characteristics of the remaining 531 subjects are shown in Table 1. The 29 sites were located in the following states of Australia: New South Wales (12), Victoria (7), Queensland (4), Western Australia (4), South Australia (1) and Tasmania (1). Nine sites were major regional centres which provided 343 of the 531 patients (65%). Fifty percent of the patients were treated in private practice, 31% were hospital-based public patients and the remainder were hospital-based private patients.

Demographics and disease characteristics for the 531 study subjects are summarised in Table 1. The mean age was 75 years (range 41 to 97 years), and there was a slight male preponderance (Table 1). The age and gender of the subjects, duration since diagnosis and baseline serum ALP were consistent across the small and large centres. The median serum ALP at time of diagnosis (based on data from 80% of subjects for whom data were available) was 221 IU/L (range 50–3070).

Details of the treatments administered to the 531 subjects between 2000 and 2005 are shown in Table 2. Fifty percent of subjects received only oral bisphosphonates during the study period, whereas 32% were treated with intravenous agents and 18% with both. The most commonly used drugs were pamidronate, alendronate and risedronate. One hundred and fifty-two subjects (29%) received treatment with two or more bisphosphonates during the study period, whereas the remaining 379 subjects received one or more courses of a single drug. A total of 1072 courses of treatment were recorded, comprising pamidronate 363 (34%), alendronate 324 (30%), risedronate 208 (19%), tiludronate 103 (10%), zoledronic acid 69 (6%) and etidronate 5 (<1%). No patient was treated with salmon calcitonin. The most recent treatment for each subject (the primary endpoint) was oral therapy in 57% of cases (alendronate 29%, risedronate 24%, and tiludronate 4%) and intravenous therapy in 43% (pamidronate 33%, and zoledronic acid 10%).

Details of treatment courses

For alendronate, the approved dose of 40 mg daily was prescribed in 258 of 322 treatment courses (80%) for which dosage was recorded, whereas 70 mg weekly (or equivalent) was prescribed 11% of courses and other doses in the remaining 9%. In subjects receiving 40 mg daily, the most frequent

Table 3
Duration of treatment in treatment courses where the approved dose of oral bisphosphonate was prescribed

Duration of treatment (months)	Alendronate 40 mg daily		Risedronate 30 mg daily		Tiludronate 400 mg daily	
1	20	9%	19	12%	11	16%
2	12	5%	**99**	**64%**	11	16%
3	27	12%	15	10%	**32**	**46%**
4	16	7%	5	3%	2	3%
5	12	5%	3	2%	4	6%
6	**86**	**38%**	5	3%	3	4%
7–12	33	15%	5	3%	5	7%
>12	21	9%	4	3%	1	1%

The data shown are number and percentage of treatment courses (not patients). The recommended duration of treatment (shown in bold) is 6 months for alendronate, 2 months for risedronate and 3 months for tiludronate.

Table 4
Dose of pamidronate administered per infusion and interval between infusions

	Interval between pamidronate infusions													
	<3 months		3 months		4 months		6 months		12 months		>12 months		Total	
Dose														
30 mg	8	2%	13	3%	3	1%	19	4%	10	2%	10	2%	63	14%
60 mg	14	3%	83	18%	13	3%	80	17%	56	12%	42	9%	288	63%
90 mg	5	1%	11	2%	16	3%	27	6%	18	4%	12	3%	89	19%
Other	2	0%	4	1%	3	1%	8	2%	1	0%	2	0%	20	4%
Total	29	6%	111	24%	35	8%	134	29%	85	18%	66	14%	460	100%

The data shown are number and percentage of infusions. In Australia, the approved dose of pamidronate for the treatment of Paget's disease is 60 mg, which can be repeated when clinically indicated.

duration of treatment was 6 months, but this accounted for only 38% of courses, with 38% of subjects receiving treatment for less than 6 months and 24% for longer than that (Table 3). Of 263 treatment courses for which both dosage and duration were recorded, only 86 (33%) were at the recommended dosage and duration of 40 mg daily for 6 months.

For risedronate, the recommended dose of 30 mg daily was prescribed in 171 of 198 of treatment courses (86%) for which dosage was recorded, whereas 30 mg weekly was prescribed in 9 (5%) and 35 mg weekly in 6 (3%) courses. In subjects receiving 30 mg daily, the duration of treatment was most commonly 2 months (64% of courses), with 12% of courses being shorter and 24% longer than 2 months (Table 3). Of 165 treatment courses for which both dosage and duration were recorded, 99 (60%) were at the recommended dosage and duration of 30 mg daily for 2 months.

For tiludronate, the approved dose of 400 mg daily was prescribed in 70 of 91 treatment courses (77%) for which dosage was recorded, whereas in 16 courses (18%), 200 mg daily was prescribed. In subjects receiving 400 mg daily, the duration of treatment was most commonly 3 months (43% of courses), whereas 32% of courses were shorter and 21% longer than this (Table 3). Of 90 treatment courses for which both dosage and duration were recorded, only 26 (29%) were at the recommended dosage and duration of 400 mg daily for 3 months.

Pamidronate was most commonly administered at a dose of 60 mg (63% of infusions), although infusions of 30 mg and 90 mg were also used (Table 4). The interval between infusions ranged widely from 1 month to more than a year, but was most commonly 6 months (29%), 3 months (24%) or 12 months (18%). The most frequent dosing schedules were 60 mg administered 3 monthly (18%), 6 monthly (17%) or annually (12%). When the data were analysed by courses of treatment (defined as above) the mean (±SD) duration of a treatment course was 9.2±12.6 months (range 1 to 55 months) and the mean number of infusions per course was 3.4±4.3 (range 1 to 25). For 195 of 240 patients, treatment consisted of regular, ongoing pamidronate infusions during the study period, with a mean of 3 infusions per year.

Zoledronic acid was administered at a dose of 4 mg in 118 of 120 infusions (98%) administered to 59 patients, whereas 5 mg was administered in single infusions to each of two subjects. Twenty-nine subjects (49%) received a single infusion, 10 (17%) received 2 infusions and 18 subjects (31%) received 3 or more infusions, whereas in 2 subjects the number of infusions was unclear. In subjects treated more than once, the interval between treatments was most commonly 3 months or 12 months.

Criteria for stopping and starting treatment

The most common reasons stated for starting a course of treatment were symptoms (72% of treatment courses) and biochemistry values (54%) (Table 5). Together, these two

Table 5
Reasons stated for starting and ending 1067 courses of treatment

	Alendronate	Risedronate	Tiludronate	Pamidronate	Zoledronic acid	All
	N=324	*N*=208	*N*=103	*N*=363	*N*=69	*N*=1067
Reason for starting treatment						
Biochemistry results	54%	64%	60%	48%	45%	54%
X-ray	22%	17%	22%	17%	12%	19%
Bone scan	30%	27%	24%	24%	36%	27%
Symptoms	71%	72%	79%	75%	59%	72%
Reason for stopping treatment						
ALP normalised	34%	27%	23%	14%	41%	25%
End of course	43%	56%	62%	58%	41%	52%
Lack of efficacy	3%	3%	3%	4%	0%	3%
Adverse events	10%	6%	10%	1%	4%	6%
Patient choice	4%	7%	5%	1%	1%	4%
Not applicable: ongoing treatment	17%	13%	12%	16%	22%	16%

Data are percentage of treatment courses for which a specific reason was listed (note that more than reason could be listed for each course). Data for etidronate (5 courses) are not included.

Table 6
Stated reasons for stopping treatment in courses of oral bisphosphonate which were shorter, longer or of the recommended duration for treating Paget's disease

	Alendronate				Risedronate				Tiludronate			
Treatment duration (months)	<6	6	>6	*P*	<2	2	>2	*P*	<3	3	>3	*P*
Number of courses	87	86	54		19	99	37		22	32	15	
ALP normalised	46%	49%	41%	0.64	16%	37%	38%	0.18	23%	38%	13%	0.19
End of course	46%	78%	43%	<0.001	42%	81%	49%	<0.001	55%	91%	27%	<0.001
Lack of efficacy	2%	1%	6%	0.28	5%	3%	5%	0.77	0%	3%	7%	0.49
Adverse events	24%	3%	4%	<0.001	37%	3%	5%	<0.001	32%	3%	7%	<0.01
Patient choice	10%	1%	4%	0.02	53%	2%	3%	<0.001	23%	0%	0%	<0.01
Ongoing treatment	1%	2%	4%	N/A	0%	3%	3%	N/A	0%	0%	40%	N/A

The table includes only treatment courses which were at the recommended dosage (alendronate 40 mg daily, risedronate 30 mg daily, and tiludronate 400 mg daily). Note that more than reason for stopping could be listed for each course. For consistency with Table 5, subjects with ongoing treatment at the time of audit are included. *P* value refers to the reason for stopping treatment, comparing shorter, standard and longer courses by chi-square testing. N/A, not applicable.

criteria accounted for the stated indications for 83% of treatment courses, but biochemistry was never listed as the sole criterion for initiating treatment. The most common reasons for ending a course of treatment were completion of a standard course (52%) and normalisation of serum ALP (25%) (Table 5). There were no major differences evident in the reasons for starting and stopping courses between different treatments, with the exception of stopping treatment because of adverse events, which was more common with alendronate (10%) and tiludronate (10%) than the other agents ($P<0.001$).

In view of the high frequency of oral bisphosphonate courses which were inconsistent with published guidelines, we examined the reasons for stopping treatment in courses which were longer or shorter than recommended, restricting the analysis to courses of alendronate, risedronate and tiludronate at the approved dosage for Paget's disease (Table 6). For treatment courses which were shorter than recommended, adverse events and patient choice were a significantly frequent reason to stop treatment than for standard courses, and this was true of all three drugs. However, in a substantial proportion of shorter courses, completion of a course and/or normalisation of ALP were given as the reason for stopping treatment. In particular, for courses of alendronate lasting three months, the most frequent indications for stopping were normalisation of ALP (59%) and end of course (52%), whereas stopping because of adverse events was infrequent (7%). For treatment courses which were longer than recommended, the most commonly stated reasons for stopping treatment were normalisation of ALP and completion of a course.

We hypothesized that longer courses of treatment might have been used in patients with more severe disease. However, baseline serum ALP did not differ significantly between subjects receiving longer or shorter courses compared with those receiving standard courses of alendronate, risedronate or tiludronate, suggesting that this was not the case.

Patient characteristics and type of treatment

To explore reasons for the use of intravenous versus oral treatment, patients were divided into three groups: those who received oral treatment only during the study period, those who received intravenous treatment and those who received both. There was no significant difference in gender, age, age at diagnosis, number of years since diagnosis, baseline serum ALP, number of bone sites affected or distribution of disease between the three groups. The only major difference between the groups was the treatment setting, in that a greater proportion of patients who received oral therapy only were managed in community-based private practice (66%) compared with those who received intravenous agents only (38%) or both oral and intravenous agents (33%) ($P<0.001$).

Clinician questionnaire

The questionnaire regarding the clinical management of Paget's disease of bone was completed by 34 clinicians, including 7 physicians (5 endocrinologists and 2 rheumatologists) who did not participate in the case note review. The results are summarised in Tables 7 and 8. Symptoms of Paget's disease was the most frequently listed criterion used to initiate treatment (94% of respondents). Pain was listed by most respondents as the most relevant symptom, and deformity and neural impingement were also listed by some respondents. Radiographic and isotope bone scan results were also commonly used to determine the need for treatment: disease location was

Table 7
Clinical criteria used to initiate treatment, markers used to monitor disease and frequency of review of patients with disease in remission according to questionnaires in which clinicians were asked to select one or more options from a checklist

		N=34
Clinical criteria used to initiate treatment		
Symptoms	32	94%
Increased alkaline phosphatase	28	82%
X-ray findings	25	74%
Bone scan results	28	82%
Clinical markers used to monitor patients		
Alkaline phosphatase	34	100%
Symptoms	33	97%
X-ray	12	35%
Bone resorption marker	10	30%
Bone scan	9	26%
Frequency of review of patients in remission		
3 monthly	2	6%
6 monthly	13	38%
Annually	16	47%
Only when symptomatic	3	9%

Table 8
Relative importance of clinical triggers for re-treatment and criteria for determining choice of intravenous or oral treatment in patients with Paget's disease

	N	Mean rank	SD
Clinical criteria triggering re-treatment			
Clinical relapse (recurrent pain or other symptom)	33	1.4	0.5
Biochemical relapse	33	1.7	0.7
Radiological relapse	26	2.8	0.7
Other	10	2.9	1.1
Criteria determining choice of intravenous or oral treatment			
Intolerance of oral therapy	33	2.3	1.6
Patient preference	32	3.3	1.6
Improved compliance	32	4.0	1.7
Lack of response to oral therapy	32	4.2	1.7
Need for rapid response	31	4.7	2.6
Ease of access to iv treatment in hospital setting	31	4.9	2.3
Lack of response to iv therapy	29	5.9	2.2
Cost	32	6.5	1.9

Investigators were asked to rank the items in order of importance, such that a rank of 1 indicated the most important item. *N*, number of investigators specifying a rank for that item.

specifically listed by 20 clinicians (59%), with involvement of skull, spine, long bones or the presence of osteolytic lesions commonly listed as indications for treatment. Age of the patient (e.g. less than 50 years) and bone resorption markers were listed by a few clinicians as relevant factors.

All respondents used plasma or serum ALP to monitor disease activity and treatment response, and all but one respondent also used symptoms to monitor patients. Twelve respondents used plain radiography for monitoring, and of these 7 stated that this was only if osteolytic lesions were present at baseline. Isotope bone scans were used by 9 respondents for disease monitoring, but this was qualified by 2 respondents as only applicable to patients with normal ALP activity. When remission of disease had been achieved, most clinicians followed patients up either every 6 or every 12 months.

When clinicians were asked to rank in order the clinical criteria which triggered re-treatment, the highest ranking items were clinical relapse, biochemical relapse and radiological relapse (Table 8). Clinical relapse of disease was ranked first by 19 respondents (58%), biochemical relapse by 10 respondents (30%) and an additional 4 respondents ranked clinical and biochemical relapse equal first. As regards the factors determining the choice between intravenous or oral treatment, intolerance of oral therapy was ranked highest followed by patient preference, whereas cost was the lowest ranking criterion.

Discussion

This study is the first to examine the management of Paget's disease of bone by specialists in the area of bone and mineral disorders. We found that in many respects, management of Paget's disease was consistent with published guidelines, but there were areas of divergence, particularly in dosage and duration of oral bisphosphonate treatment.

The most commonly used drugs were pamidronate, alendronate and risedronate. Tiludronate was used less commonly, etidronate rarely, and calcitonin not at all. This is broadly consistent with the UK guidelines for management of Paget's disease which recommend against the routine use of calcitonin or etidronate in favour of pamidronate, risedronate or tiludronate [2] and with the ASBMR guidelines, which recommend that calcitonin, etidronate or tiludronate be reserved for patients who are intolerant of more potent bisphosphonates [1,6]. With regard to pamidronate treatment schedules, the UK guidelines recommend either three infusions of 60 mg or six infusions of 30 mg at intervals of two weeks [2], whereas in the United States, the FDA-approved regimen is 30 mg daily for three days [1]. None of these regimens was commonly used in the study, with the most frequently used regimens being 60 mg every 3, 6 or 12 months. This diversity in clinical practice with regard to pamidronate treatment may reflect the wide range of regimens that have been published [10–22], and the fact that in Australia, the product information recommends a dose of 60 mg but makes no recommendation on dosing frequency or interval.

With regard to the oral bisphosphonates, the most striking finding was the widespread use of non-standard courses. For risedronate, the majority of courses were at the approved dose and duration, but this was not true for either alendronate or tiludronate. Adverse events and patient choice were common reasons for stopping treatment courses which were shorter than recommended, and appeared significantly more common with alendronate and tiludronate than risedronate. In other cases, however, the non-standard duration of treatment courses appeared to be based on clinical efficacy and clinician choice, with normalisation of ALP frequently stated as the reason for terminating courses which were either shorter or longer than recommended. There is some evidence to support this. For example, although a 6 month course of alendronate is recommended, there is evidence that 3 months treatment is effective in Paget's disease of mild to moderate severity [21,25] and that continuing treatment beyond 6 months may be appropriate for more severe disease [21]. That said, the use of prolonged courses of high dose bisphosphonate for durations in excess of 12 months (observed in 9% of alendronate courses in the survey) is of some concern, as the safety of such regimens is not established. For example, occasional cases of osteonecrosis of the jaw have been associated with prolonged, high dose bisphosphonate treatment for Paget's disease [26].

The survey period preceded the publication in late 2005 of a key clinical trial demonstrating superiority of zoledronic acid to risedronate for the treatment of Paget's disease of bone [23]. Despite this, zoledronic acid was administered off-label to 11% of subjects, in most cases as an infusion of 4 mg, which is approved for oncology indications.

Perhaps unsurprisingly, it appeared that patients were more likely to receive oral bisphosphonate treatment if they were managed in community-based private practice than if attending a hospital clinic. Having said that, the community-based setting was not a complete barrier to the use of intravenous therapy, with approximately a third of patients administered parenteral therapy in that setting. The results of the questionnaire suggested that the main factors determining clinicians' choice of intravenous versus oral therapy were in fact patient preference and concerns regarding tolerability of

and compliance with oral bisphosphonates. The results of both the case note review and the clinician questionnaire suggest that the main reasons for initiating treatment were symptoms, disease activity and disease distribution. This is consistent with both sets of published guidelines [1,2] but only partly consistent with the Australian Pharmaceutical Benefits Schedule, which subsidises treatment only for symptomatic patients regardless of anatomical location or activity.

The strengths of this study include its large sample size and its nationwide, multi-centre, stratified design, which means that the results are likely to be representative of the clinical practice of specialist physicians with an interest in Paget's disease in Australia. The study also has limitations. The participating physicians were mainly endocrinologists and rheumatologists associated with teaching hospitals, and we do not know if the results reflect the clinical practice of other specialists such as geriatricians or general physicians. As with all surveys, we cannot be certain that responses to the clinician questionnaire reflect clinical practice in reality, although the consistency between the results of the case note review and responses to the questionnaire is reassuring. A weakness of the study is that serum ALP was not systematically recorded for treatment courses, leading to some uncertainty as to how appropriate or otherwise the duration of treatment was in some patients.

In conclusion, we report the results of a national survey of the management of Paget's disease by Australian specialist physicians with an interest in metabolic bone disease. To a large extent, clinical practice is consistent with published clinical guidelines. However, the widespread use of oral bisphosphonate treatment courses which are not at the approved dose or duration raises concern that the management of this disorder in everyday clinical practice may not be optimal.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bone.2008.01.024.

References

[1] Lyles KW, Siris FR, Singer FR, Meunier PJ. A clinical approach to diagnosis and management of Paget's disease of bone. J Bone Miner Res 2001;16:1379–87.

[2] Selby PL, Davie MW, Ralston SH, Stone MD. Guidelines on the management of Paget's disease of bone. Bone 2002;31:366–73.

[3] Walsh JP. Paget's disease of bone. Med J Aust 2004;181:262–5.

[4] Whyte MP. Paget's disease of bone. N Engl J Med 2006;355:593–600.

[5] Roodman GD, Windle JJ. Paget disease of bone. J Clin Invest 2005;115:200–8.

[6] Siris ES, Lyles KW, Singer FR, Meunier PJ. Medical management of Paget's disease of bone: indications for treatment and review of current therapies. J Bone Miner Res 2006;21(Suppl 2):P94–8.

[7] Siris E, Weinstein RS, Altman R, Conte JM, Favus M, Lombardi A, et al. Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. J Clin Endocrinol Metab 1996;81:961–7.

[8] Reid IR, Nicholson GC, Weinstein RS, Hosking DJ, Cundy T, Kotowicz MA, et al. Biochemical and radiologic improvement in Paget's disease of bone treated with alendronate: a randomized, placebo-controlled trial. Am J Med 1996;101:341–8.

[9] 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.

[10] Adami S, Salvagno G, Guarrera G, Montesanti F, Garavelli S, Rosini S, et al. Treatment of Paget's disease of bone with intravenous 4-amino-1-hydroxybutylidene-1,1-bisphosphonate. Calcif Tissue Int 1986;39:226–9.

[11] Cantrill JA, Buckler HM, Anderson DC. Low dose intravenous 3-amino-1-hydroxypropylidene-1,1-bisphosphonate (APD) for the treatment of Paget's disease of bone. Ann Rheum Dis 1986;45:1012–8.

[12] Harinck HI, Papapoulos SE, Blanksma HJ, Moolenaar AJ, Vermeij P, Bijvoet OL. Paget's disease of bone: early and late responses to three different modes of treatment with aminohydroxypropylidene bisphosphonate (APD). BMJ 1987;295:1301–5.

[13] Vega E, Gonzalez D, Ghiringhelli G, Mautalen C. Intravenous aminopropylidene bisphosphonate (APD) in the treatment of Paget's bone disease. J Bone Miner Res 1987;2:267–71.

[14] Thiebaud D, Jaeger P, Gobelet C, Jacquet AF, Burckhardt P. A single infusion of the bisphosphonate AHPrBP (APD) as treatment of Paget's disease of bone. Am J Med 1988;85:207–12.

[15] Stone MD, Hawthorne AB, Kerr D, Webster G, Hosking DJ. Treatment of Paget's disease with intermittent low-dose infusions of disodium pamidronate (APD). J Bone Miner Res 1990;5:1231–5.

[16] Fenton AJ, Gutteridge DH, Kent GN, Price RI, Retallack RW, Bhagat CI, et al. Intravenous pamidronate in Paget's disease: clinical, biochemical, histomorphometric and radiological responses. Clin Endocrinol (Oxf) 1991;34:197–214.

[17] Ryan PJ, Sherry M, Gibson T, Fogelman I. Treatment of Paget's disease by weekly infusions of 3-aminohydroxypropylidene-1,1-bisphosphonate (APD). Br J Rheumatol 1992;31:97–101.

[18] Watts RA, Skingle SJ, Bhambhani MM, Pountain G, Crisp AJ. Treatment of Paget's disease of bone with single dose intravenous pamidronate. Ann Rheum Dis 1993;52:616–8.

[19] Gutteridge DH, Ward LC, Stewart GO, Retallack RW, Will RK, Prince RL, et al. Paget's disease: acquired resistance to one aminobisphosphonate with retained response to another. J Bone Miner Res 1999;14(Supp 2):79–84.

[20] Trombetti A, Arlot M, Thevenon J, Uebelhart B, Meunier PJ. Effect of multiple intravenous pamidronate courses in Paget's disease of bone. Rev Rhum Engl Ed 1999;66:467–76.

[21] Walsh JP, Ward LC, Stewart GO, Will RK, Criddle RA, Prince RL, et al. A randomized clinical trial comparing oral alendronate and intravenous pamidronate for the treatment of Paget's disease of bone. Bone 2004;34:747–54.

[22] Merlotti D, Gennari L, Martini G, Valleggi F, De Paola V, Avanzati A, et al. Comparison of different intravenous bisphosphonate regimens for Paget's disease of bone. J Bone Miner Res 2007;22:1510–7.

[23] Reid IR, Miller P, Lyles K, Fraser W, Brown JP, Saidi Y, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med 2005;353:898–908.

[24] Hosking D, Lyles K, Brown JP, Fraser WD, Miller P, Curiel MD, et al. Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. J Bone Miner Res 2007;22:142–8.

[25] Khan SA, Vasikaran S, McCloskey EV, Beneton MN, Rogers S, Coulton L, et al. Alendronate in the treatment of Paget's disease of bone. Bone 1997;20:263–71.

[26] Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, et al. American Society for Bone and Mineral Research. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007;22:1479–91.