JBMR

Randomized Trial of Intensive Bisphosphonate Treatment Versus Symptomatic Management in Paget's Disease of Bone

Anne L Langston,[1,2] Marion K Campbell,[3] William D Fraser,[4] Graeme S MacLennan,[3] Peter L Selby,[5] and Stuart H Ralston[1,2] for the PRISM Trial Group

[1]Rheumatic Diseases Unit, Institute of Genetics and Molecular Medicine University of Edinburgh, United Kingdom
[2]Edinburgh Clinical Trials Unit, University of Edinburgh, United Kingdom
[3]Health Services Research Unit, University of Aberdeen, United Kingdom
[4]Department of Clinical Biochemistry, University of Liverpool, United Kingdom
[5]Department of Medicine, University of Manchester, United Kingdom

ABSTRACT

Bisphosphonates are widely regarded as the treatment of choice for Paget's disease of bone (PDB) because of their potent inhibitory effects on bone turnover, but the effects of bisphosphonate therapy on symptoms and complications of PDB have been little studied. Here we report the results of a randomized trial that compared the effects of symptomatic treatment with intensive bisphosphonate therapy in a cohort of 1324 patients with PDB who were followed up for a median of 3 years (range 2 to 5 years). The symptomatic treatment group was treated only if they had pagetic bone pain, for which they were first given analgesics or anti-inflammatory drugs, followed by bisphosphonates if they did not respond. The intensive group received repeat courses of bisphosphonates irrespective of symptoms with the aim of reducing and maintaining serum alkaline phosphatase (ALP) levels within the normal range. The endpoints were fracture, orthopedic surgery, quality of life, bone pain, and hearing thresholds. Serum ALP levels were significantly lower in the intensive treatment group than in with the symptomatic treatment group within 4 months of commencing treatment and remained lower throughout the study ($p < .001$). There was no difference between the groups in quality of life (as assessed by the SF36 questionnaire), in overall bodily pain, or in pagetic bone pain. Hearing thresholds, as assessed by audiometry did not change significantly and did not differ between the treatment groups. Clinical fractures occurred in 46 of 661 patients (7.0%) in the intensive treatment group compared with 49 of 663 patients (7.4%) in the symptomatic treatment group, and orthopedic surgery was required in 50 of 661 patients (7.3%) in the intensive treatment group and in 55 of 663 patients (8.3%) in the symptomatic treatment group. These differences were not significant. Subgroup analyses of patients with elevated ALP levels at baseline and those who did or did not receive bisphosphonates during the study yielded similar results to those in the study group as a whole. We conclude that striving to maintain normal ALP levels with intensive bisphosphonate therapy confers no clinical advantage over symptom-driven management in patients with established PDB. Neither management strategy had a significant beneficial impact on pain or quality of life (Clinical trial registration number ISRCTN12989577). © 2010 American Society for Bone and Mineral Research.

KEY WORDS: CLINICAL TRIAL; PAGET'S DISEASE OF BONE; BISPHOSPHONATE; FRACTURE

Introduction

Paget's disease of bone (PDB) is a common disorder that affects up to 2% of Caucasians aged over 55 years that is characterized by increased osteoclastic bone resorption coupled with increased and disorganized bone formation at one or more sites throughout the skeleton.[1] Up to 30% of patients develop complications such as bone deformity, pathologic fracture, deafness, and secondary osteoarthritis[2] that adversely affect quality of life.[3,4] Bisphosphonates are considered to be the treatment of choice for PDB because they are highly effective at suppressing the elevated bone turnover that is characteristic of the disease.[5–7] Many experts believe that bisphosphonate therapy should be administered with the aim of normalizing bone turnover in the hope that this will arrest disease progression and prevent the development of complications.[7,8] While several potent bisphosphonates are now licensed for the treatment of PDB,[5,6,9] clinical trials of these agents mainly have been explanatory studies focusing on highly selected subgroups of patients who have been evaluated with respect to short-term

Submitted for publication on 11 September 2008. Accepted in revised form on 10 April 2009. Published ahead of print on 6 July 2009.
Address correspondence to: Professor Stuart H Ralston, Molecular Medicine Centre, Western General Hospital, Edinburgh EH2 SX4, United Kingdom.
E-mail: stuart.ralston@ed.ac.uk

Journal of Bone and Mineral Research, Vol. 25, No. 1, January 2010, pp 20–31
DOI: 10.1359/jbmr.090709

responses of biochemical markers such as alkaline phosphatase (ALP).[5,6,9–12] Previous studies of bisphosphonate therapy in PDB have failed to evaluate the effects of treatment on disease progression or complications, and few investigators have documented treatment effects on quality of life. Here we performed a pragmatic clinical trial in which we compared the effects of intensive bisphosphonate therapy with those of symptomatic treatment on clinical outcome and complications of Paget's disease. Pragmatic trials differ from explanatory trials in that they measure the effectiveness of interventions in routine clinical practice because they aim to inform clinicians about the risks and benefits of different treatment strategies.[13] The aim of the study was to determine if intensive bisphosphonate therapy aimed at reducing and/or maintaining ALP levels within the normal range conferred any clinical benefit over symptom-driven treatment of patients with PDB.

Method

Study design and power

The Paget's disease: randomized trial of intensive versus symptomatic management (PRISM) study was a pragmatic randomized, controlled trial designed to compare the effects of two management strategies on fracture, quality of life, bodily pain, and other common complications of PDB, including the requirement for orthopedic surgery and hearing loss. Clinical fractures were chosen as the primary endpoint with which to power the study because this was the only clinical outcome for which any prospective data were available in patients with PDB.[10,14] Secondary outcomes included quality of life, bodily pain, bone pain, progression of hearing loss, orthopedic surgical procedures, and serum ALP levels. The study was powered to detect a 50% relative reduction in fractures in the intensive treatment group (with 89% power at an alpha of 5%) assuming that fracture rate would be in the region of 2.4 per 100 patient-years, as reported previously.[2,15] The reason for choosing this degree of reduction in fracture rate was that bisphosphonates have been reported to reduce the incidence of clinical fractures by about 50% in osteoporosis,[16] and we assumed that the antifracture effects in PDB might be similar. The PRISM study was an event-driven trial. We calculated that 90 fractures would be required to meet the primary endpoint. To achieve this aim, we originally planned to enroll 1500 patients and follow them for 2.5 years. During the trial, the actual fracture rate was higher than expected (2.93 fractures per 100 patient-years). In view of this, the number of patients was reduced, but the duration of follow-up increased such that we enrolled 1324 patients and followed them up for a median of 3 years (range 2 to 4 years) to give a treatment exposure of 3239 patient-years. A total of 95 fractures occurred, which gave the study 93.8% power to meet the primary endpoint. The study had greater than 99% power to detect a clinically significant (5-point) difference in quality-of-life scores (as assessed by the Medical Outcomes Study 36 Item Short-Form Health Survey [SF36]), 88% power to detect a 0.5 standard deviation difference in hearing thresholds (as assessed by audiometry), and 97% power to detect a 50% reduction in the requirement for orthopedic surgery.

Recruitment

Recruitment was based in 39 secondary referral centers in the United Kingdom. Patients were invited to take part in the study if they were known to have PDB diagnosed by standard clinical criteria,[17] were considered by the attending clinician to be able to adhere to the study protocol, and had a life expectancy of greater than 1 year. No specific exclusion criteria were applied on the basis of treatment history, baseline serum total ALP levels, or coexisting disease. In total, 2110 patients with PDB were assessed for eligibility between December 2001 and June 2004. Of these subjects, 149 (7.0%) were ineligible, and 630 (29.8%) were eligible but were not recruited (Fig. 1). Eligible patients who were not recruited were slightly older than trial participants (mean $\pm$ SD age $= 78 \pm 9.0$ years), and the proportion of males was slightly lower ($n = 291$, 46.1%) than in the final study population. The reasons for nonrecruitment were patient declined ($n = 533$, 84.6%), clinician chose not to recruit ($n = 21$, 3.3%), patient not approached ($n = 9$, 1.4%), patient leaving the country ($n = 4$, 0.6%), and other reasons ($n = 63$, 10%).

Randomization and treatment

Patients were assigned to the treatment groups by an integrated telephone and Web-based randomization system. Treatment allocation employed minimization[18] to ensure that the treatment groups were balanced with respect to key prognostic variables. Minimization criteria were ALP values at baseline (within normal range, elevated up to twice the upper limit of normal, or elevated more than twice the upper limit of normal), previous bisphosphonate treatment (yes or no), presence of the disease in a weight-bearing lower limb (yes or no), bone deformity (yes or no), skull involvement (yes or no), and bone pain (yes or no). The study was not blinded. The attending clinicians were instructed to follow two distinct management strategies, as depicted in Fig. 2. In the symptomatic treatment group, clinicians were instructed to give no treatment for PDB unless the patient had bone pain. Patients who experienced pain were treated initially with analgesics or nonsteroidal anti-inflammatory drugs (NSAID), and antiresorptive therapy was administered only if the response to these treatments was inadequate. In this case, clinicians were instructed to use tiludronate, etidronate, or subcutaneous calcitonin as the treatments of first choice. Aminobisphosphonates also were permitted in this group but only when the response to the others was considered inadequate. Within the intensive treatment group, clinicians were instructed to give bisphosphonate therapy irrespective of symptoms, with the aim of restoring or maintaining ALP levels within the reference range. For patients with raised ALP levels at baseline, physicians were advised to give bisphosphonate treatment as required to reduce ALP levels to normal. For patients with normal ALP levels at baseline, clinicians were advised to give bisphosphonate treatment if serum ALP values became elevated during follow-up. Bisphosphonate use also was permitted as a preemptive measure in patients in whom serial measurements of ALP had shown a rising trend, and values were in the upper quartile of the reference range. The use of any licensed bisphosphonate was permitted, but risedronate was chosen as the first-line treatment because this was the most

potent bisphosphonate available at the time when the study began.[19] Other bisphosphonates were used when risedronate caused adverse effects, where problems were encountered with compliance, or where risedronate did not give a satisfactory biochemical response. In all cases, drug treatments were administered according to the approved dosing regimens. Risedronate was given orally in a dose of 30 mg daily for 2 months. In the case of pamidronate, different strategies were used in the different treatment groups. In the intensive treatment arm, pamidronate 60 mg was given by intravenous infusion on three occasions to a total dose of 180 mg. In the symptomatic treatment arm, a single infusion of 30 mg pamidronate was administered initially, and further infusions of 30 mg were given until a response occurred to a maximum of 180 mg. Tiludronate was given orally in a dose of 400 mg daily for 3 months, and etidronate was given orally in a dose of 400 mg daily for 3 to 6 months. Calcitonin was given subcutaneously in a dose of 50 to 100 units daily for up to 3 months. A few patients were treated with clodronate orally in a dose of 800 mg daily for 3 months or intravenously in a dose of 300 mg daily on three to five occasions. Within the intensive treatment arm, antiresorptive treatment was repeated after an interval of 4 months in patients who had not achieved normalization of ALP. Within the symptomatic arm, repeated treatment was only given to control bone pain that was resistant to painkillers.

Adherence to treatment

Adherence to treatment was assessed directly by collecting information on the treatment received at each study visit. We were also able to assess adherence to antiresorptive therapy indirectly by measurement of serum ALP levels, which are a well-established biochemical marker of metabolic activity and response to antiresorptive therapy in PDB.

Study endpoints

The primary endpoint of the study was clinical fracture. Fracture data were specifically collected on participant case-record forms at each clinic visit, and visits were scheduled at 4-monthy intervals during the study. The diagnosis of fracture was validated by clinicians at the participating centers by examination of hospital case records, records of general practitioners, and X-ray films and radiology reports. Secondary endpoints were quality of life as assessed by several validated instruments (see below), progression of hearing loss as assessed by audiometry, and the requirement for orthopedic surgery. Serum total ALP was measured according to standard techniques, and the values were normalized to the upper limit of the local laboratories' reference range so that results could be compared across centers. Quality of life was assessed by the Stanford Health Assessment Questionnaire Disability Index[20] (HAQ), the Euro-QoL questionnaire (EQ-5D), the Medical Outcomes Study 36 Item Short-Form Health Survey (SF36) questionnaire,[21] and the arthritis-specific version of the SF36 (ASHI).[22] All individual domain scores of the SF36 were normalized to a mean of 50, as described in the SF36 Scoring Manual.[21] The ASHI scores were calculated from the SF36 data[22] and were not normalized. Patients with skull involvement were invited to undergo audiometry, and hearing thresholds were established at 0.5, 1, 2, 3, and 4 kHz for each ear at baseline and at the end of the study. A high pure-tone average for air conduction was calculated as the arithmetic mean of the pure-tone threshold.

Clinical assessments

The extent of skeletal involvement was assessed by radionuclide bone scan, which was performed routinely at study entry, unless a bone scan had been performed within 10 years prior to enrollment. The attending physician was asked to clinically assess whether the patient had evidence of bone deformity using a 3-point scale as follows: 0 = no deformity; 1 = mild/moderate deformity; and 2 = severe deformity. Patients were asked if they had bone pain or not, and physicians were asked to assess whether they considered that the bone pain reported was due to PDB. The most common criteria used by physicians for assigning bone pain to Paget's disease were localization of pain to an affected site, response of pain at that site to previous treatment with bisphosphonate, pain at rest, and pain at night. Information was collected on previous bisphosphonate treatment, whether such treatment had been given during the previous year, previous fracture, orthopedic surgery, and history of osteosarcoma.

Statistical analysis

Primary statistical analysis was based on the intention-to-treat principle and included all available data. Descriptive data are expressed as number and percentages or means $\pm$ SD as appropriate unless otherwise stated. Differences between the intervention groups were assessed by logistic regression, analysis of covariance, Cox regression, or chi squared test as appropriate. Estimates of effect sizes are presented with 95% confidence intervals (CIs). All analyses were adjusted for minimization variables.

Ethics

All participants gave written informed consent to be included in the study. The trial was approved by the UK Multicentre Research Ethics Committee for Scotland (MREC01/0/53), by local ethical review boards in the participating study centers, and by the Medicines & Healthcare Products Regulatory Authority (CTA 21583/0002/001-0001). The study was included in the controlled clinical trials register (*www.controlled-trials.com*) and assigned the reference number ISRCTN12989577.

Results

Characteristics of study population

The trial design is shown in Fig. 1, and demographic characteristics are shown in Table 1. The treatment groups were closely matched at baseline with regard to all relevant clinical variables. Most participants had polyostotic disease, and use of a hearing aid was reported at baseline in 22% of participants. Bone deformity was present in about 36% of participants, 39% had previously suffered a clinical fracture, 16% had required orthopedic surgery, and approximately 70% had been treated

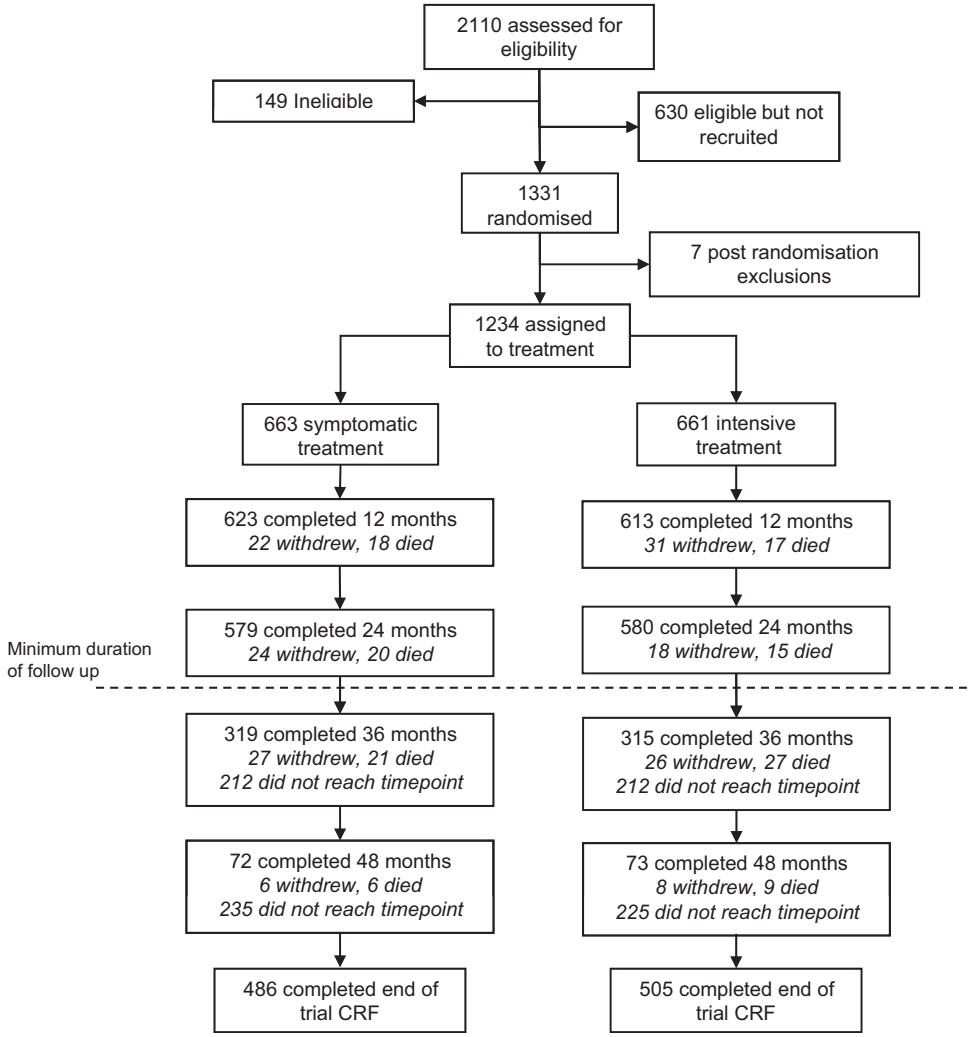

Fig. 1. Randomization, treatment, and outcome.

previously with bisphosphonate therapy. At baseline, ALP levels were normal in just over half the patients in each treatment group. During the study, however, biochemical relapse occurred in 78 of 349 patients (22.3%) in the intensive treatment group and 92 of 358 patients (25.6%) in the symptomatic treatment group in patients with initially normal ALP levels. As reported previously,[4] we found no significant association between biochemical control of PDB (as reflected by baseline levels of ALP) and quality of life assessed by the SF36 physical summary and mental summary scores (data not shown).

Treatment received

The treatment algorithm is shown in Fig. 2. Bisphosphonates were administered to 500 of 661 patients in the intensive treatment arm (75.6%) and to 331 of 663 patients (49.9%) in the symptomatic treatment arm ($p < .001$). Patients in the intensive treatment arm who received bisphosphonates during the trial had higher levels of ALP at baseline (mean $\pm$ SD = 139% $\pm$ 99%, where 100% is the upper limit of normal) compared with those who did not receive bisphosphonates (105% $\pm$ 119%, $p < .001$). Corresponding values in the symptomatic treatment arm were 153% $\pm$ 154% (received bisphosphonates) compared with 124% $\pm$ 127% (never received bisphosphonates, $p = .008$). A significantly higher proportion of patients in the intensive treatment group received risedronate (61.9% versus 20.4%, $p < .001$), whereas use of tiludronate (15.1% versus 2.9%, $p < .001$) and etidronate (4.5% versus 2%, $p = .008$) was significantly greater in the symptomatic group. Analgesics, NSAIDs, and treatments for neuropathic pain were used by all patients at some point in the trial in both treatment groups. However, certain classes of painkillers were used more commonly in symptomatic treatment arm. For the individual drug classes, the proportion of patients in each group who received at least one prescription was as follows (symptomatic versus intensive): paracetamol (77.7% versus 73.4%, $p = .069$), NSAIDs (73.3% versus 61.9%, $p < .001$), codeine/dihydrocodeine (50.1% versus 48.0%, $p = .44$), compound analgesics (42.4% versus 38.4%, $p = .14$), opiates (19.0% versus 15.0%, $p = .051$), and antineuropathic agents (0.8% versus 1.2%, $p = .40$).

Serum alkaline phosphatase

The response of ALP is shown in Fig. 3. There was a significant reduction in ALP within 4 months in the intensive treatment group, and ALP levels remained suppressed throughout the

Table 1. Baseline Characteristics of Patients

	Symptomatic ($n = 663$)	Intensive ($n = 661$)
Male	341 (51.4%)	354 (53.5%)
Age at enrolment (years)	74 ± 8	73 ± 9
Age at diagnosis (years)	66 ± 11	66 ± 11
Monostotic	240 (36.2%)	233 (35.2%)
Affected bones		
Skull	157 (23.7%)	155 (23.4%)
Spine	249 (37.6%)	265 (40.1%)
Pelvis	428 (64.6%)	456 (69.0%)
Femur	215 (32.4%)	214 (32.4%)
Tibia	127 (19.2%)	118 (17.9%)
Hearing aid	151 (22.9%)	144 (21.9%)
Normal ALP at baseline	358 (54.0%)	349 (52.8%)
Biochemical relapse during follow-up[a]	92/347 (26.5%)	78/343 (22.7%)
Serum total ALP[b]	139 ± 149	131 ± 105
Serum creatinine (μmol/L)	95.5 ± 25.6	95.8 ± 29.8
Any bone pain[c]	460 (69.4%)	451 (68.2%)
Bone pain owing to Paget's[d]	304 (66.1%)	314 (69.6%)
Bone deformity	242 (36.5%)	233 (35.2%)
Previous fracture	268 (40.4%)	250 (37.8%)
Previous surgery for Paget's disease	113 (17.0%)	99 (15.0%)
Previous bisphosphonate therapy	462 (69.7%)	469 (71.0%)
Bisphosphonates in the last 12 months	195 (29.4%)	191 (28.9%)
Family history of PDB	91 (13.7%)	92 (13.9%)
SF-36 Questionnaire		
Physical functioning	34.0 ± 12.5	35.1 ± 12.5
Role physical	37.9 ± 12.2	39.1 ± 12.3
Bodily pain	39.2 ± 11.2	40.0 ± 10.7
General health	42.5 ± 10.8	42.8 ± 10.3
Vitality	44.1 ± 11.5	44.6 ± 11.2
Social functioning	42.0 ± 12.9	43.0 ± 12.8
Role emotional	41.5 ± 14.6	42.6 ± 14.5
Mental health	48.5 ± 11.0	48.6 ± 10.9
Physical summary	35.8 ± 11.3	36.7 ± 11.3
Mental summary	48.6 ± 11.8	48.7 ± 11.8
Stanford Health Assessment Questionnaire		
Standard Disability Index	0.99 ± 0.79	0.96 ± 0.79
Alternative Disability Index	0.77 ± 0.73	0.76 ± 0.72

Values are mean ± standard deviation or number (%).

[a]Patients with normal ALP at baseline who developed raised ALP during follow-up. Number of patients who had normal ALP. There was no significant difference between the groups for any variable.

[b]Serum total ALP values are expressed as relative to the upper limit of the reference range, which is set at 100%.

[c]Patient reported bone pain.

[d]Bone pain considered by the clinician to be due to Paget's disease, expressed as a percentage of those experiencing bone pain.

study. ALP also decreased in the symptomatic treatment arm, and the difference was significant from 12 months. The proportion of patients in the intensive treatment group with ALP within the reference range was 83.9% at year 1, 81.0% at year 2, and 78.8% at the end-of-study visit. The proportion of patients with ALP within the reference range in the symptomatic treatment arm was 62.4% at year 1, 63.2% at year 2, and 61.2% at the end-of-study visit.

Quality of life

Quality-of-life data were collected by questionnaire at baseline and annually thereafter. No significant differences were found between the treatment groups in response of the SF36 physical summary score, mental summary score, and bodily pain (Fig. 4) or any of the other individual subcategory scores from the SF36 assessment (data not shown). Analysis of the data using other quality-of-life instruments, including the HAQ score, the EuroQoL 5D, and the ASHI similarly showed no difference between the intensive and symptomatic treatment groups at any time point (data not shown).

Fractures and requirement for orthopedic surgery

There was no difference in fracture rate between the groups. Fractures that occurred in bones affected by PDB were less

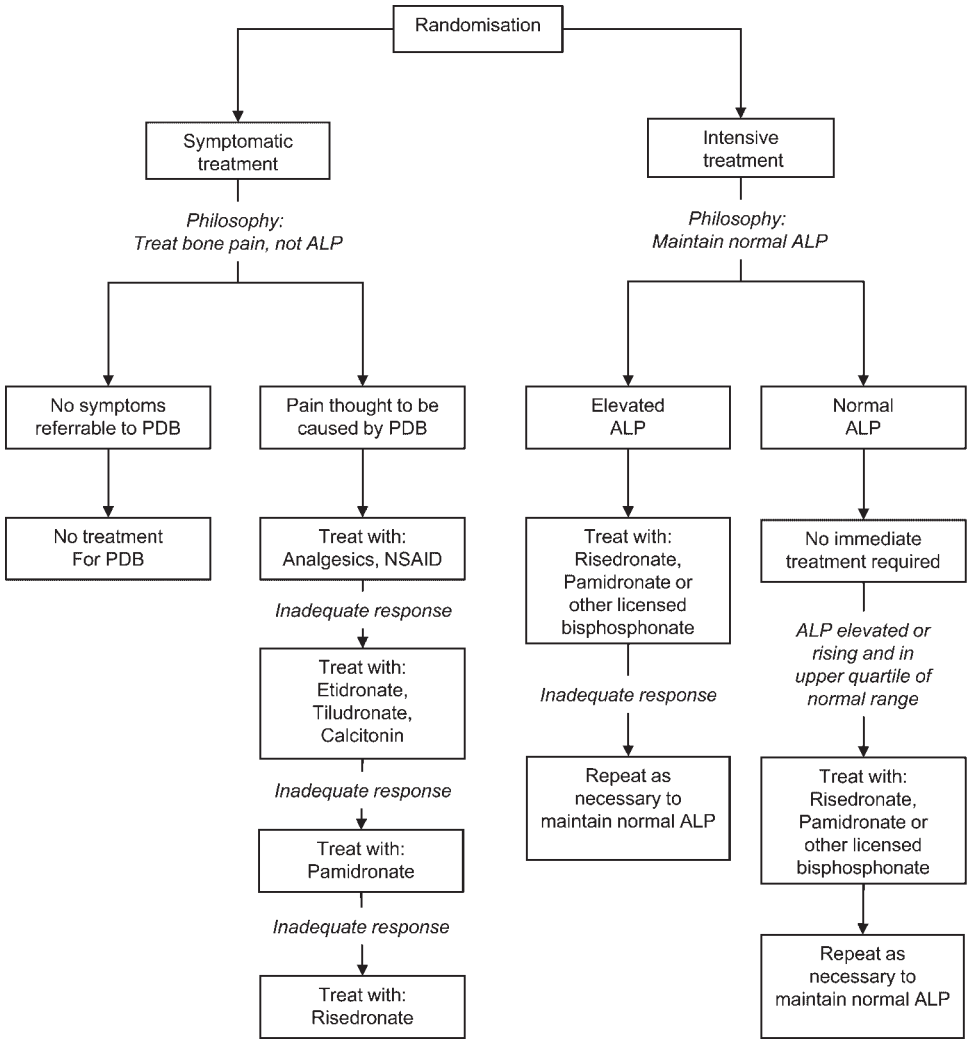

Fig. 2. Treatment algorithm in symptomatic and intensive treatment groups. The treatment algorithm is shown in both groups. As indicated, analgesics and/or NSAIDs were used as an initial measure to control pain before bisphosphonate therapy had been given in the symptomatic treatment group but also were used after bisphosphonate therapy for pain control. All patients in both groups received painkillers at some point during the study.

common in the intensive treatment group, but these only accounted for 19% of clinical fractures that occurred during the study, and the difference between the groups was not significant (Table 2). A time-to-event analysis with correction for minimization variables showed no difference in fracture rates between the treatment groups (data not shown). During the study, 103 patients (7.7%) required orthopedic surgery, most because of osteoarthritis of the knee or the hip (see Table 2). There was no significant difference between the treatment groups in the proportion of patients who required orthopedic surgery.

Hearing loss

At the baseline visit, 295 of 1324 (22.2%) individuals used a hearing aid, and the proportion was higher (267 of 991, 26.9%) at the end of the study ($\chi^2 = 6.7$, $p = 0.01$). The proportion of hearing aid users in the symptomatic treatment group (133 of 486, 27.3%) was not significantly different from the proportion in the intensive treatment group at the end of the study (134 of 505, 26.5%, $p = .76$). Audiograms were performed in 413 ears from patients who had skull involvement at baseline, and these were repeated in 334 ears at the end of the study. Paired audiograms before and after the study were obtained in 224 ears. Analysis of paired audiogram data showed no significant decrease in hearing thresholds during the study and no significant difference between the groups (Fig. 5). The pattern of hearing loss was predominantly sensorineural. Sensorineural deafness of moderate severity or worse was detected in 211 ears (51.8%), pure conductive deafness was found in 3 ears (0.07%), and mixed conductive and sensorineural deafness was found in 16 ears (3.8%).

Bone pain

The response of bone pain is summarized in Table 3. There was no significant change in the proportion of patients who experienced bone pain between baseline and follow-up at 2 years in either group. The proportion of patients with bone pain attributed to PDB fell significantly between baseline and follow-up at 2 years in both groups, but there was no difference between the groups. The fall in prevalence of pagetic bone pain was counterbalanced by a significant increase in bone pain attributed to causes other than PDB.

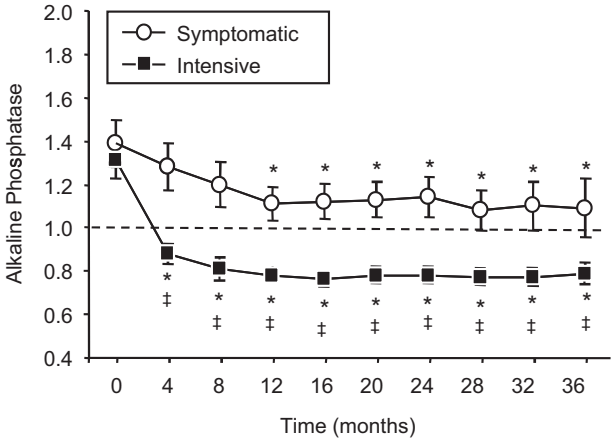

Fig. 3. Effects of treatment on alkaline phosphatase. (*A*) Response of alkaline phosphatase values normalized to the upper limit of the reference range for each center, which was set to a level of 1.0. Values are means, and bars are 95% confidence intervals (CIs), and the upper limit of normal is indicated by a horizontal interrupted line. The groups were significantly different ($p < .001$) from 4 months onward. *Significant change ($p < .05$ or less) from baseline. ‡Significant difference ($p < .001$) between groups.

Adverse events

A total of 6900 adverse events occurred during the study, but these were distributed evenly in the two treatment groups (3471 symptomatic versus 3429 intensive). Serious adverse events also were distributed evenly (359 symptomatic versus 345 intensive). There was no significant difference in the type or rate of adverse events according to body systems between the treatment groups (Table 4), and no cases of osteonecrosis of the jaw were reported. Cardiac arrhythmia was reported as an adverse event in 7 of 663 patients (1.0%) in the symptomatic treatment group and in 13 of 661 patients (1.9%) in the intensive treatment group, a difference that was not significant ($\chi^2 = 1.84$, $p = 0.17$).

Subgroup analyses

Since many of the patients enrolled into PRISM study had advanced disease and had been treated previously with bisphosphonates, we performed an exploratory subgroup analysis to study the effects of intensive and symptomatic treatment on patients with metabolically active disease. At baseline, 707 patients (53.4%) had elevated ALP values. There was no difference between the treatment groups in this subgroup of patients with respect to fractures, requirement for orthopedic surgery, hearing thresholds, pain, or quality of life (Table 5). Since bisphosphonate therapy was permitted in both groups, a further subgroup analysis was performed in which we compared the responses in patients who had received bisphosphonates during the trial with the responses of those who did not (Table 6). This showed no significant difference between the groups, although the rate of fracture and orthopedic surgery was noted to be slightly higher in patients who received bisphosphonates.

Discussion

PDB is a common condition that negatively affects quality of life[3,4] owing to the occurrence of various complications such as bone deformity, bone pain, osteoarthritis, hearing loss, and fracture.[2,23] Bisphosphonates have been investigated widely in the treatment of PDB,[24] but virtually all studies have been short term and have used serum ALP levels as the primary outcome measure rather than clinical endpoints.[5,6,12,14,25] While ALP

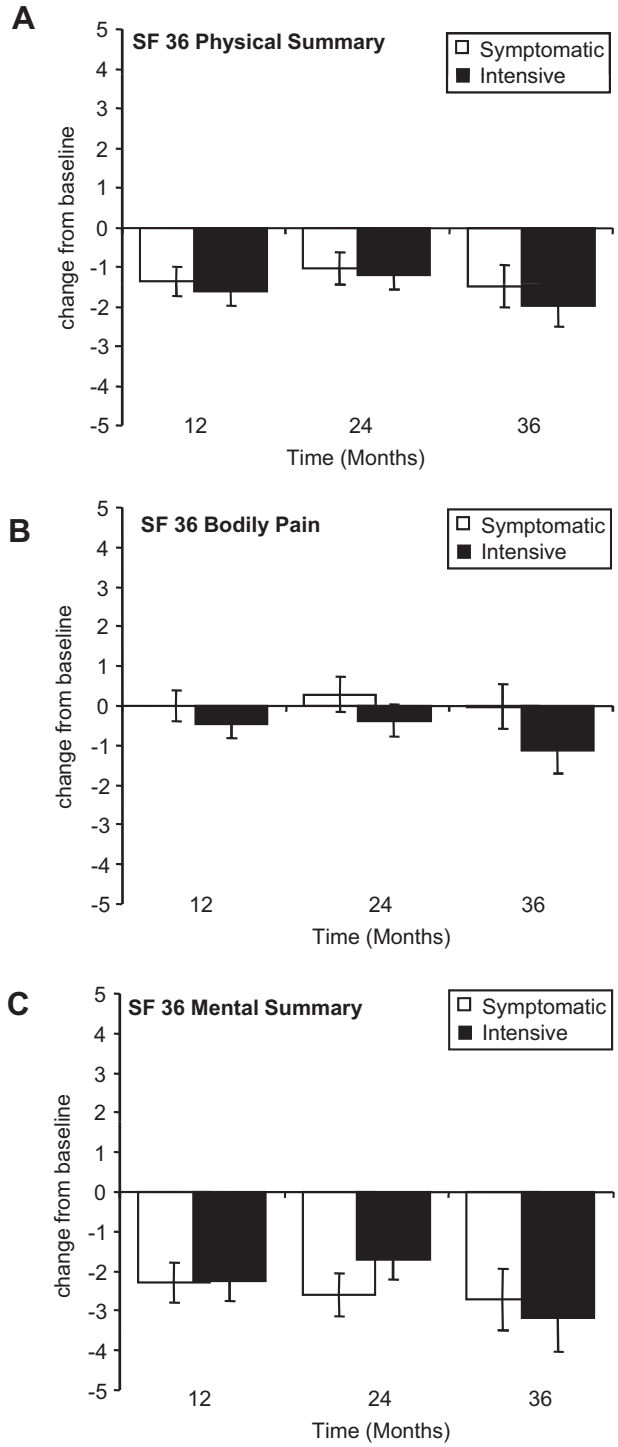

Fig. 4. Effects of symptomatic and intensive treatment on quality of life. (*A*) Response of physical summary score as assessed by SF36 questionnaire. (*B*) Response of bodily pain as assessed by SF36 questionnaire. (*C*) Response of mental summary score as assessed by SF36 questionnaire. Values are means, and bars are SEM. There was no significant difference between the treatment groups at any time point.

Table 2. Effects on Fracture and Requirement for Orthopedic Surgery

	Symptomatic ($n = 663$)	Intensive ($n = 661$)	Effect size (95% CI)
Participants with fracture[a]	49 (7.4%)	46 (7.0%)	0.97 (0.65–1.46)
Total fractures[b]	55	51	0.93 (0.62–1.39)
Fracture through pagetic bone[b]	13	8	0.62 (0.22–1.60)
Clinical vertebral fracture[b]	12	10	0.83 (0.32–2.10)
Participants requiring orthopedic surgery[a]	55 (8.3%)	48 (7.3%)	0.86 (0.57–1.32)
Number of procedures[b]	63	50	0.79 (0.54–1.17)
Knee arthroplasty[b]	16	12	0.75 (0.32–1.69)
Hip arthroplasty[b]	24	24	1.00 (0.55–1.84)
Others[b]	23	14	0.61 (0.29–1.24)

Values are numbers and percentages. Effect sizes are hazard ratios or rate ratios and 95% CIs for individual outcomes based on the number events that occurred during the study.

[a]Hazard ratio from Cox regression.

[b]Incidence-rate ratio based on 1621 person-years of follow-up in the symptomatic arm and 1618 person-years in the intensive arm.

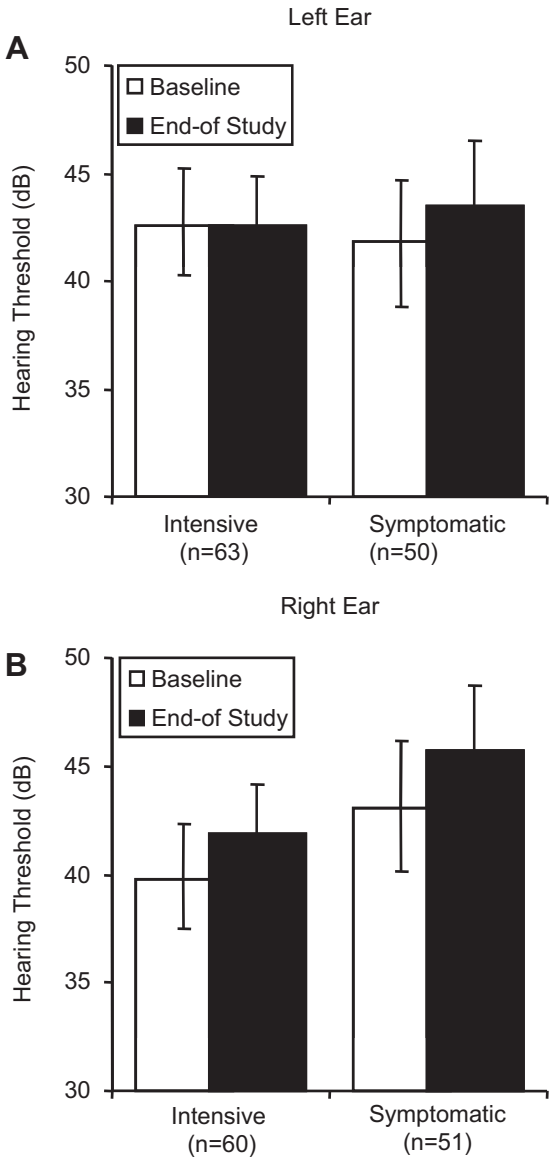

Fig. 5. Effects of treatment on hearing thresholds. (*A*) Paired audiometry data before and after the study from the left ear. (*B*) Data from the right ear. Columns are means, and bars are SEM. There was no significant difference in hearing threshold between the treatment groups.

levels are a recognized marker of metabolic activity in PDB, there is no evidence that patients with lower levels of ALP have a more favorable clinical outcome.[4]

The effects of bisphosphonates on complications of PDB have been little studied. Untreated patients with PDB can go on to develop progressive bone deformity,[26] but PDB also has been reported to progress in about one-third of patients despite treatment with etidronate.[27] Etidronate seldom normalizes bone turnover in PDB, however,[1] and over recent years, more potent bisphosphonates have been developed that can normalize bone turnover in a high proportion of patients.[28–30] This has raised the hope that these new drugs might be more effective in arresting disease progression of PDB and in preventing complications,[7,8] but the long-term effects of these agents on clinical outcome of PDB have not been studied adequately.

The aim of the PRISM study was to determine whether suppression of metabolic activity with bisphosphonate therapy offers any clinical advantage over symptom-directed treatment in patients with established PDB. As expected, intensive bisphosphonate therapy was significantly more effective at suppressing ALP levels than symptomatic treatment, but this was not accompanied by a difference in pain control between the treatment groups. These observations are consistent with the results of previous smaller studies that have shown a poor correlation between the reduction in ALP levels and the response of pain in PDB. For example, risedronate and alendronate both have been shown to be more effective than etidronate at suppressing ALP levels in PDB, but they give similar responses in terms of bone pain.[5,6] In another study, alendronate was highly effective at reducing ALP levels in PDB but was no more effective than placebo at controlling pain.[12] This might be due to the fact that pain in PDB sometimes occurs as the result of increased bone turnover but also can be caused by complications of the disease such as osteoarthritis, bone deformity, and nerve compression syndromes that do not respond well to bisphosphonate therapy. Although there was no significant difference in bodily pain or pagetic pain between the treatment groups, the use of NSAIDs was slightly but significantly higher in the symptomatic treatment group. This suggests that intensive bisphosphonate therapy probably does have a beneficial effect

Table 3. Effects of Treatment on Bone Pain

	Symptomatic	Intensive	χ^2, p value
Any bone pain (Baseline)	460/663 (69.7%)	451/661 (68.2%)	0.2, .65
Any bone pain (2 years)	311/422 (73.7%)	295/423 (69.7%)	1.6, .20
Pagetic bone pain (baseline)	304/460 (66.1%)	314/451 (69.6%)	1.3, .25
Pagetic bone pain (2 years)	96/311 (30.8%)*	78/295 (26.4%)*	1.45, .22
Nonpagetic bone pain (baseline)	156/460 (33.9%)	137/451 (30.4%)	1.25, .25
Nonpagetic bone pain (2 years)	215/311 (69.1%)*	217/295 (73.5%)*	1.45, .22

*$p < .0001$ significantly different from baseline (assessed by chi-squared test). The χ^2 and p values refer to the comparison between treatment groups at each time point.

Table 4. Adverse Events and Serious Adverse Events

	Symptomatic	Intensive
Total adverse events	3471	3429
Serious adverse events	359	345
Musculoskeletal	734	691
Sensory	196	203
Gastrointestinal	157	172
Cardiovascular	327	360
Cancer	47	55
Renal	78	98
Other	1932	1850

Number of events in each major category is shown. There was no significant difference in adverse event or serious adverse event profile in patients treated with intensive and symptomatic therapy.

at controlling pain owing to PDB but that similar results can be obtained by increased use of analgesics supplemented with on-demand bisphosphonate therapy in patients who do not respond adequately.

An interesting finding to emerge from this study is that the prevalence of pagetic bone pain as defined by physicians fell in both groups during the study, whereas the prevalence of nonpagetic bone pain increased. We believe that the most likely explanation for this is the fact that physicians commonly use response to bisphosphonate therapy as one of the markers of pagetic bone pain. Since the PRISM study was not blinded, and since many patients in both groups received bisphosphonates, it could be that any reductions in pain that did occur were deemed to due to bisphosphonate therapy. Although this raises the possibility that the beneficial effects on pagetic bone pain observed in the symptomatic group also were attributable to bisphosphonate therapy, against this is that fact that we observed no difference in pain control overall in subgroup analysis of patients who received bisphosphonates as compared with those who did not. The increased frequency of nonpagetic bone pain that occurred in both groups is intriguing, but the underlying reasons are unclear. A possible explanation could be the occurrence of bisphosphonate-induced musculoskeletal pain, which is a recognized adverse effect of bisphosphonate therapy.[31,32] However, other possible reasons would be progression of preexisting problems such as osteoarthritis and bone deformity.

We found no significant difference between the treatment groups in occurrence of clinical fractures overall or in the requirement for orthopedic surgery. While this excludes the possibility that intensive bisphosphonate therapy reduces fracture rate and the requirement for surgery by 50% in PDB when compared with symptomatic treatment, lesser reductions cannot be confidently excluded. There was a trend in favor of a reduction in rates of pagetic fracture, but this was not statistically significant. However, it should be acknowledged that pagetic fractures were uncommon, and the power to detect a treatment effect was limited. The observations presented here indicate that a study of 5000 patients followed for 3 years would be required

Table 5. Subgroup Analysis According to Baseline Alkaline Phosphatase Values

	Symptomatic		Intensive	
	Normal ALP	Raised ALP	Normal ALP	Raised ALP
Bodily pain	$n = 358$	$n = 305$	$n = 349$	$n = 312$
Baseline	38.0 ± 10.4	40.7 ± 12.0	40.0 ± 10.3	40.1 ± 11.1
+12 months	38.6 ± 10.0	41.2 ± 11.2	40.0 ± 10.0	40.1 ± 10.6
+24 months	38.8 ± 10.4	41.4 ± 11.0	40.1 ± 10.8	40.6 ± 10.5
+36 months	37.8 ± 9.2	41.7 ± 11.0	39.6 ± 10.9	40.6 ± 10.4
Physical summary score				
Baseline	34.6 ± 10.7	37.3 ± 11.8	36.9 ± 10.37	36.5 ± 12.0
+12 months	34.4 ± 10.2	36.4 ± 11.3	35.9 ± 10.5	37.0 ± 11.3
+24 months	34.9 ± 10.5	36.6 ± 11.6	36.4 ± 10.9	36.5 ± 11.2
+36 months	34.1 ± 10.5	36.5 ± 10.9	36.5 ± 11.0	36.1 ± 10.8
Fracture	28 (8.9%)	21 (7.5%)	28 (6.6%)	18 (8.0%)
Orthopedic surgery	32 (7.8%)	23 (6.9%)	23 (8.0%)	25 (5.8%)

The values are means $\pm$ standard deviation for the SF36 bodily pain score and physical summary score and numbers and percentages for fractures and orthopedic surgery. There was no significant difference between the subgroups at any time point for any variable.

Table 6. Subgroup Analysis According to Use of Bisphosphonate Therapy

	No bisphosphonate	Bisphosphonate
Bodily pain	$n = 493$	$n = 831$
Baseline	40.7 ± 11.4	38.9 ± 12.0
+12 months	41.5 ± 10.8	39.1 ± 11.2
+24 months	41.6 ± 11.1	39.3 ± 11.0
+36 months	40.6 ± 11.2	39.4 ± 11.0
Physical summary score		
Baseline	37.6 ± 11.6	35.3 ± 11.0
+12 months	37.2 ± 10.8	35.1 ± 11.7
+24 months	37.9 ± 11.3	34.9 ± 10.8
+36 months	37.5 ± 11.5	34.9 ± 10.4
Fracture	28 (5.0%)	67 (8.8%)
Orthopedic surgery	34 (6.1%)	69 (9.0%)

The values are means ± standard deviation for the SF36 bodily pain score and physical summary score and numbers and percentages for fractures and orthopedic surgery. There was no significant difference between the subgroups at any time point for any variable.

to detect a significant effect of intensive treatment on pagetic fractures, assuming that such an effect exists. Although there are few prospective data on fracture rates in PDB, it is of interest that the frequency of clinical fractures that we observed in the PRISM study is similar to that reported in epidemiologic studies[2,23] and in a previous placebo-controlled study of patients with PDB.[10]

Deafness is an important complication of PDB, and the presence of disease in the skull is considered by many experts to be an indication for antiresorptive therapy in the hope that this might prevent progression of hearing loss.[7] However, the effects of bisphosphonate therapy on progression of hearing loss have not been studied previously. In the PRISM trial, hearing thresholds remained relatively stable during follow-up, with no difference between the treatment groups. Although hearing aid use increased overall during the study, this could have been the result simply of the fact that the study population was aging. While we cannot exclude the possibility that intensive treatment could have an effect on progression of deafness in the long term, there is certainly no evidence for a beneficial effect in the medium term.

Quality of life is substantially reduced in patients with PDB who are being treated in a secondary-care setting,[4] and in this study, the baseline SF36 physical summary scores were about 15 points below those expected in the general population. Neither intensive therapy nor symptomatic therapy had a significant impact on quality of life during the study, and there was no significant difference between the treatment groups. These results differ somewhat from those in the HORIZON study, where zoledronic acid was found to be superior to risedronate at improving some aspects of quality of life in PDB, including bodily pain.[9] The individual changes in the HORIZON study were modest, however, and were generally below the 5-point threshold that is considered clinically significant. It is possible that the greater potency of zoledronic acid may have contributed to this difference because in the PRISM study we were able to normalize ALP levels in only 80% of patients, which was similar to that achieved in the risedronate arm of the HORIZON study.[9] It also should be noted, however, that HORIZON was a short-term study, and it remains unclear if the early beneficial effects of zoledronic acid on quality of life were maintained beyond the initial 6-month period of follow-up.

Our ability to detect a difference between the treatment strategies could have been limited by the fact that patients with normal ALP values were included in the study and because bisphosphonates were prescribed to some patients in the symptomatic treatment group. Subgroup analyses were performed in order to address this issue, but these showed no difference in response when patients were stratified according to baseline ALP levels or according to whether bisphosphonates were administered or not. Furthermore, the intention-to-treat analysis also failed to show a difference between the treatment strategies, and this took into account the fact that many patients had normal baseline ALP levels.

It also might be argued that intensive treatment was not appropriate in patients with normal ALP levels at baseline. Although we acknowledge that immediate bisphosphonate therapy was not necessary in these patients, intensive treatment was required subsequently in 22% because of biochemical relapse, whereas in the symptomatic treatment group, biochemical relapse was not actively treated without adverse clinical consequences.

While the PRISM study provided no evidence to support the view that intensive bisphosphonate treatment improves clinical outcome in established PDB, this does not exclude the possibility that benefits may exist in certain subgroups of patients. The duration of follow-up in the PRISM study is longer than in any previous trial of bisphosphonate therapy in PDB, but we acknowledge that complications develop slowly,[26] and the duration of follow-up may have been too short to observe benefit. Another limitation is that that most patients had advanced disease. It could be that intensive treatment is more likely to be effective in bisphosphonate-naive subjects or in patients with early disease, and this is an area that merits further study. An important strength of PRISM is that it is the only trial that was specifically designed to examine the effects of treatment on complications and quality of life in PDB and is about 10 times larger than the next biggest study.[33]

The only significant difference in clinical outcome to emerge was that patients in the symptomatic treatment arm had a significantly greater requirement for NSAID than patients in the intensive treatment arm. This might be considered advantageous because of the potential for adverse events in association with increased NSAID use, but we observed no difference in type or number of adverse events between the treatment groups. There is also the potential for adverse effects such as osteonecrosis of the jaw,[34] cardiac arrhythmia,[35,36] and subtrochanteric fractures[37] to occur in association with the high doses of bisphosphonates that were used in the intensive treatment arm, but we did not observe any of these complications in this study. The incidence of cardiac arrhythmia in the intensive treatment group was double that of the symptomatic treatment group, but the total number of events was small, and the difference between the groups was not significant. In view of this, it looks as though the risks and benefits of the two therapeutic approaches used in this study are

roughly equivalent, at least over the time frame used in this study. Longer-term follow-up will be required to evaluate if differences eventually might emerge between the treatment strategies groups, and the PRISM study is currently being extended for a further three years to address this issue.

Clinical guidelines for the management of PDB have drawn attention to the fact that the evidence base is inadequate with regard to the effects of treatment on complications and long-term clinical outcome.[17] The results of the PRISM study highlight the fact that current approaches to management have a very limited impact on quality of life, hearing loss, and pain. This highlights the need for further studies to rigorously examine the effects of bisphosphonates in patients with early PDB to evaluate whether the impressive effects of these agents on accelerated bone turnover and osteolytic lesions[12] can be translated into clinical benefits for patients.

Disclosures

Stuart H Ralston acts as a consultant for Procter & Gamble, Novartis, and Merck. William D Fraser acts as a consultant for Procter & Gamble, MSD, Novartis, Sanofi Aventis, Nycomed, and Roche. Peter L Selby is a consultant for Procter & Gamble, Novartis, Nycomed, and Roche. Anne L Langston has received a travel bursary from Procter & Gamble and Sanofi-Aventis. All other authors state that they have no conflicts of interest. Risedronate is marketed jointly by Proctor & Gamble and Sanofi-Aventis for the treatment of Paget's disease. Etidronate is marketed by Proctor & Gamble for the treatment of Paget's disease. Tiludronate is marketed by Sanofi-Aventis for the treatment of Paget's disease. Zoledronic acid is marketed by Novartis for the treatment of Paget's disease.

Acknowledgments

We wish to thank all the participants without whose help and enthusiasm this study would never have succeeded. Thanks are also due to staff at the trial coordinating office: Gary Adams (data manager), Daniel Barnett (trial programmer), Marie Cameron (research assistant), Janice Cruden (data manager), Magnus McGee (trial statistician), Donna Patterson (data manager), Clare Robertson (research assistant), Allan Walker (trial programmer), and Euan Wiseman (trial programmer), as well as to staff at the local collaborating hospitals whose help made this study possible. Thanks to the independent trial steering committee: Maarten Boers (chair), Juliet Compston, Philip Hannaford, Marilyn McCallum, and R Graham Russell and to the Data Monitoring Committee: Ernest Choy (chair 2001–2006), Sarah Hewlett, and Chris Roberts. Special thanks also to Dr. Ian Mackenzie and Dr. Tim Bowden for assistance with the analysis of audiograms.

Author Contributions

Professor Ralston had full access to all the data in the study and takes responsibility for integrity of the data and accuracy of the data analysis. *Study concept and design:* Ralston and Campbell. *Acquisition of data:* Ralston, Langston, and Campbell. *Analysis and interpretation of data:* Ralston, Campbell, Langston, MacLennan, Selby, and Fraser. *Drafting of the manuscript:* Langston, Ralston, and MacLennan. *Critical revision of the manuscript for important intellectual content:* Ralston, Campbell, Langston, MacLennan, Selby, and Fraser. *Statistical analysis:* MacLennan and Ralston. *Obtaining funding:* Ralston, Campbell, Selby, and Fraser. *Study supervision:* Langston, Ralston, and Campbell.

Members of the PRISM Research Group

Clinical Centers: Aberdeen Royal Infirmary, United Kingdom, Vera Herd, Stuart H Ralston*; University Hospital Aintree, United Kingdom, Rose McIver, Mashood Siddiqi*; Royal National Hospital for Rheumatic Disease, Bath, United Kingdom, Ashok Bhalla,* Diana Cochran, Sharon Grieve, Sara Mills; Musgrave Park Hospital, Belfast, United Kingdom, Katrina Hughes, Richard Wallace*; Queen Elizabeth Hospital, Birmingham, United Kingdom, Neil Gittoes*, Liz McGregor; Royal Bolton Hospital, United Kingdom, Keatley RH Adams,* Mary Adams; Ninewells Hospital, Dundee, United Kingdom, Vera Herd, Graham Leese*, Ellen Malcolm; University Hospital of North Durham, United Kingdom, Sarah Hailwood*; Medway Maritime Hospital, Gillingham, United Kingdom, Paul Ryan,* Gwen Worcester; Western Infirmary, Glasgow, United Kingdom, Alastair McLellan,* Debby Nelson; Huddersfield Royal Infirmary, United Kingdom, Allan Fairclough, Richard Reece*; Raigmore Hospital, Inverness, United Kingdom, Fiona McGhie, Malcolm Steven*; Airedale Hospital, Keighley, United Kingdom, Annie Cooper,* Stuart H Ralston*; Leicester Royal Infirmary and Leicester General Hospital, United Kingdom, Margaret Coe, S Javed Iqbal,* Geraldine McHugh; Royal Liverpool University Hospital, United Kingdom, William D Fraser,* Ya-Wen Jessica Huang, Margaret Little, Vinita Mishra, Nicola Wherly; Llandudno General Hospital, United Kingdom, Merle Maddison, Lyn Vaterlaws*; Guy's Hospital, London, United Kingdom, Ignac Fogelman,* Nina Prescod; King's College Hospital, London, United Kingdom, Rama Chandra, Tina Mangion, Caje Moniz*; Manchester Royal Infirmary, United Kingdom, Susan Harrison, Peter L Selby*; The James Cook University Hospital, Middlesbrough, United Kingdom, John N Fordham,* Val Lunn, Dawn Youll; Freeman Hospital, Newcastle, United Kingdom, Roger Francis*; Norfolk & Norwich University Hospital, United Kingdom, Jane Leeder, David GI Scott*; City Hospital, Nottingham, United Kingdom, David Hosking,* Pat San; Robert Jones & Agnes Hunt Orthopaedic Hospital, Oswestry, United Kingdom, Michael Davie,* Teresa Jones, Dawn Pugh; Nuffield Orthopaedic Centre, Oxford, United Kingdom, Matthew Brown, Vicky Toghill, John Wass,* Jo Young; Llandough Hospital, Penarth, United Kingdom, Roz Broadbent, Mike Stone,* Jane Turton; Derriford Hospital, Plymouth, United Kingdom, Charles Hutton,* Maggie Jolly; Poole Hospital, United Kingdom, Julia Taylor, Paul Thompson*; Harold Wood Hospital, Romford, United Kingdom, Kuntal Chakravarty*; Oldchurch Hospital, Romford, United Kingdom, Christine Heron, Christopher Kelsey*; Hope Hospital, Salford, United Kingdom, Sylvia Mercer, Terence W O'Neill*; Northern General Hospital, Sheffield, United Kingdom, Jenny Cliffe, Linda Kersh, Eugene McCloskey*; Southampton General Hospital, United Kingdom, Trish Byng, Janet

*Principal investigators at each center.

Cushnaghan, Cyrus Cooper,* Nick Harvey, Karen Walker-Bone; Royal National Orthopaedic Hospital, Stanmore, United Kingdom, Richard Keen,* Maggie Partridge; The Great Western Hospital, Swindon, United Kingdom, Lynne Kerton, Elizabeth Price*; Queen Elizabeth II Hospital, Welwyn Garden City, United Kingdom, Jill Lomas, Peter Winocour*; Arrowe Park Hospital, Wirral, United Kingdom, E George, TD Kennedy,* Anthony Lake; Yeovil District Hospital, United Kingdom, Nita Beacham, Clare Buckley, Jenny Knight, Lisa Martin, TG Palferman.*

Funding/Support

The study was supported by grants from the Arthritis Research Campaign UK (Ref. 13627), the National Association for Relief of Paget's Disease, Procter & Gamble Pharmaceuticals, and Sanofi-Aventis.

References

1. Ralston SH, Langston AL, Reid IR. Pathogenesis and management of Paget's disease of bone. Lancet. 2008;372:155–163.
2. van Staa TP, Selby P, Leufkens HG, Lyles K, Sprafka JM, Cooper C. Incidence and natural history of Paget's disease of bone in England and Wales. J Bone Miner Res. 2002;17:465–471.
3. Gold DT, Boisture J, Shipp KM, Pieper CF, Lyles KW. Paget's disease of bone and quality of life. J Bone Miner Res. 1996;11:1897–1904.
4. Langston AL, Campbell MK, Fraser WD, Maclennan G, Selby P, Ralston SH. Clinical determinants of quality of life in Paget's disease of bone. Calcif Tissue Int. 2007;80:1–9.
5. 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. Paget's Risedronate/Etidronate Study Group. Am J Med. 1999;106:513–520.
6. Siris ES, Weinstein RS, Altman R, et al. Comparative study of alendronate versus etidronate for the treatment of Paget's disease of bone. J Clin Endocrinol Metab. 1996;81:961–967.
7. Lyles KW, Siris ES, Singer FR, Meunier PJ. A clinical approach to diagnosis and management of Paget's disease of bone. J Bone Miner Res. 2001;16:1379–1387.
8. Siris ES. Goals of treatment for Paget's disease of bone. J Bone Miner Res. 1999;14:S49–52.
9. Reid IR, Miller P, Lyles K, et al. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. N Engl J Med. 2005;353:898–908.
10. Altman RD, Johnston CC, Khairi MR, Wellman H, Serafini AN, Sankey RR. Influence of disodium etidronate on clinical and laboratory manifestations of Paget's disease of bone (osteitis deformans). N Engl J Med. 1973;289:1379–1384.
11. Ralston SH, Boyce BF, Cowan RA, et al. The effect of 1,α-hydroxyvitamin D_3 on the mineralization defect in disodium etidronate treated Paget's disease: a double-blind, randomized study. J Bone Miner Res. 1987;2:5–12.
12. Reid IR, Nicholson GC, Weinstein RS, et al. Biochemical and radiologic improvement in Paget's disease of bone treated with alendronate: a randomized, placebo-controlled trial. Am J Med. 1996;101:341–348.
13. Roland M, Torgerson DJ. What are pragmatic trials? Br Med J. 1998;316:285.
14. Fraser WD, Stamp TC, Creek RA, Sawyer JP, Picot C. A double-blind, multicenter, placebo-controlled study of tiludronate in Paget's disease of bone. Postgrad Med J. 1997;73:496–502.
15. Khairi MR, Johnston CC Jr, Altman RD, Wellman HN, Serafini AN, Sankey RR. Treatment of Paget disease of bone (osteitis deformans): results of a one-year study with sodium etidronate. JAMA. 1974;230:562–567.
16. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C. Meta-analyses of therapies for postmenopausal osteoporosis: IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev. 2002;23:570–578.
17. Selby PL, Davie MW, Ralston SH, Stone MD. Guidelines on the management of Paget's disease of bone. Bone. 2002;31:366–373.
18. Altman DG, Bland JM. Treatment allocation by minimisation. Br Med J. 2005;330:843.
19. Singer FR, Clemens TL, Eusebio RA, Bekker PJ. Risedronate, a highly effective oral agent in the treatment of severe Paget's disease. J Clin Endocrinol Metab. 1998;83:1906–1910.
20. Ziebland S, Fitzpatrick R, Jenkinson C, Mowat A, Mowat A. Comparison of two approaches to measuring change in health status in rheumatoid arthritis: the Health Assessment Questionnaire (HAQ) and modified HAQ. Ann Rheum Dis. 1992;51:1202–1205.
21. Ware JE Jr, Gandek B. Overview of the SF-36 Health Survey and the International Quality of Life Assessment (IQOLA) Project. J Clin Epidemiol. 1998;51:903–912.
22. Ware JEJ, Keller SD, Hatoum HT, Kong SX. The SF-36 Arthritis-Specific Health Index (ASHI): I. Development and cross-validation of scoring algorithms. Med Care. 1999;37:MS40–50.
23. Melton LJ III, Tiegs RD, Atkinson EJ, O'Fallon WM. Fracture risk among patients with Paget's disease: a population-based cohort study. J Bone Miner Res. 2000;15:2123–2128.
24. Kanis JA. *Pathophysiology and Treatment of Paget's Disease of Bone*. 2nd Ed, 1998, Dunitz, London.
25. Roux C, Gennari C, Farrerons J, et al. Comparative prospective, double-blind, multicenter study of the efficacy of tiludronate and etidronate in the treatment of Paget's disease of bone. Arthritis Rheum. 1995;38:851–858.
26. Siris ES, Feldman F. Natural history of untreated Paget's disease of the tibia. J Bone Miner Res. 1997;12:691–692.
27. Ravault A, Meunier PJ. [Long-term follow-up of 88 patients with Paget's disease treated by discontinuous courses of low-dose disodium etidronate]. Rev Rhum Mal Osteoartic. 1989;56:293–302 [in French].
28. Siris ES, Chines AA, Altman RD, et al. Risedronate in the treatment of Paget's disease of bone: an open label multicenter study. J Bone Miner Res. 1998;13:1032–1038.
29. Arden-Cordone M, Siris ES, Lyles KW, et al. Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. Calcif Tissue Int. 1997;60:415–418.
30. Siris ES. A potent new bisphosphonate for Paget's disease of bone. Am J Med. 1996;101:339–340.
31. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. Arch Intern Med. 2005;165:346–347.
32. Bock O, Boerst H, Thomasius FE, et al. Common musculoskeletal adverse effects of oral treatment with once weekly alendronate and risedronate in patients with osteoporosis and ways for their prevention. J Musculoskel Neuronal Interact. 2007;7:144–148.
33. Hosking D, Lyles K, Brown JP, et al. Long-term control of bone turnover in Paget's disease with zoledronic acid and risedronate. J Bone Miner Res. 2007;22:142–148.
34. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med. 2006;144:753–761.
35. Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. N Engl J Med. 2007;356:1895–1896.
36. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. 2007;356:1809–1822.
37. Schneider JP. Bisphosphonates and low-impact femoral fractures: current evidence on alendronate-fracture risk. Geriatrics. 2009;64:18–23.