The use of alendronate in the treatment of avascular necrosis of the femoral head

FOLLOW-UP TO EIGHT YEARS

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The use of bisphosphonates in the treatment of avascular necrosis of the femoral head is an encouraging but relatively new option with most published data being derived from small trials with limited follow-up. We present a clinicoradiological analysis of 395 hips with avascular necrosis which were treated with oral alendronate for three years with a mean follow-up of four years (1 to 8).

Our results show an improvement in the clinical function, a reduction in the rate of collapse and a decrease in the requirement for total hip replacement, compared with the findings of other studies in which no treatment was given. This improvement is particularly marked if the treatment is begun in the pre-collapse stages of the disease. Even in Ficat stage-III hips some benefit was obtained from treatment with alendronate by at least a delay in the need for total hip replacement.

Osteonecrosis or avascular necrosis of the femoral head can cause structural failure of bone with collapse and dysfunction of the hip.¹ Collapse of the femoral head was observed in 75% of cases of avascular necrosis of the femoral head within three years of presentation by Merle d'Aubigné et al² and in 80% within four years of onset of hip pain due to avascular necrosis by Ohzono et al.³ According to Aaron et al,⁴ more than 50% of patients with avascular necrosis of the femoral head require THR within three years of diagnosis. Indeed, it is reported to be the most common cause of THR in young adults.⁵

Agarwala et al⁶ first reported the efficacy of alendronate, a bisphosphonate, in the treatment of avascular necrosis of the femoral head and showed that it not only improved the symptoms but also retarded progression of the disease and reduced the rate of collapse of the femoral head.^{7,8} Other studies have shown similar results^{9,10} and bisphosphonates are now considered to be one of the standard options of treatment for avascular necrosis of the femoral head.¹¹

We have offered alendronate as the primary line of management to all of our patients with avascular necrosis of the femoral head. We have analysed the outcome in 294 patients (395 hips) with avascular necrosis of the femoral head treated with alendronate over a period of eight years and compared our findings with known data regarding the natural history of avascular necrosis of the femoral head.

Patients and Methods

Between 1999 and 2006, we saw 434 patients with avascular necrosis of the femoral head. Of these, 48 were excluded because they already had degenerative arthritis (Ficat and Arlet stage IV¹²) and a further 63 who had concurrent peptic ulceration or hepatorenal derangement. Thus, 323 patients received alendronate, of whom ten were lost to follow-up in less than one year of starting alendronate therapy and 19 opted for surgery before completion of one year of treatment. This latter group was considered to be early failures. A minimum follow-up of one year was an inclusion criterion and 294 patients (395 hips) were included in the study. The mean age at presentation was 39.1 years (22 to 55) with 202 male and 92 female patients. The mean follow-up was four years (1 to 8) (Table I).

All the patients received 10 mg of alendronate per day with standard precautions for a period of three years along with a daily oral supplement of 500 mg to 1000 mg of calcium and of 400 IU to 800 IU of vitamin D₃. For control of pain, analgesics and non-steroidal anti-inflammatory agents were given as needed. In the first three months of treatment, all the patients were advised to use toe-touch weight-bearing when walking using elbow or axillary crutches with weight-bearing increased gradually as dictated by pain.

After the first visit, the patients were followed up every three months for the first year and

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Table I. Duration of symptoms before starting treatment and of follow-up of hips for each Ficat and Arlet stage

	Number of hips	Mean (SD, range) duration of hip pain (mths) before treatment	Mean (SD, range) follow-up (yrs)
Ficat and Arlet stage at the commencement of treatment			
I	215	7.8 (4.9, 1 to 36)	4.0 (2.2, 1 to 8)
II	129	14.7 (11.0, 2 to 48)	4.3 (2.1, 1 to 8)
III	51	25.8 (15.8, 6 to 60)	3.7 (2.1, 1 to 8)
Total	395	12.4 (11.0, 1 to 60)	4.0 (2.2, 1 to 8)

annually thereafter and also if their pain increased suddenly. The annual visits were continued even after cessation of alendronate treatment at three years. The lack of an indigenous hip functional scoring system and poor compatibility of the existing scores with the activities of daily living of Indian patients, required us to record pain and function using simple parameters. At presentation and at each follow-up visit, pain and disability scores were recorded on a verbal response scale of 0 to 10 (0 for no pain, 10 for the most severe) while time for which continuous standing could be tolerated during activities of daily living and maximum uninterrupted walking time were recorded in minutes. The duration of hip pain before starting treatment was recorded while at follow-up visits, the consumption of analgesics and the side-effects of the drug, if any, were also noted. All the data recorded were compared with the corresponding parameters at previous visits and discussed with the patients to encourage adherence to this long-term daily treatment.

Plain anteroposterior (AP) pelvic radiographs were repeated at every visit. The Ficat and Arlet¹² staging of the femoral head was reported by an independent blinded radiologist. The duration of symptoms at presentation and the results are shown in Table I. Financial constraints prevented MRI being performed in all the patients and it was reserved for patients with suspected Ficat stage-I avascular necrosis of the femoral head.

Patients were considered to be lost to follow-up if they did not attend for their annual visit up to six months after their appointment despite reminders by telephone. Some patients were lost to follow-up after a few regular annual visits and the clinicoradiological data recorded before this are included in the present analysis.

Clinical failure was defined as deterioration on the basis of pain/disability scores and standing or walking time, severe enough to require THR. The hips which did not fail were considered to be survived hips. Radiological progression was defined as worsening of the radiological appearance by one grade or more on the Ficat and Arlet scale and was considered to be a radiological failure. Radiological collapse was defined as progression of the Ficat stage I or II to Ficat stage III.

Post-treatment hips comprised the subgroup of patients who had been followed up for a minimum of one year (1 to 5) after having completed the three-year course of alendronate treatment. A comparison with the available

historical data of clinical failure and radiological progression was undertaken in all the hips available including the post-treatment hip subgroup to evaluate any after-effect of the treatment.

Statistical analysis. The mean values of the pain, disability scores and standing and walking times at various time intervals were compared with those at presentation. The Wilcoxon signed-rank test was used as the test of significance between groups after confirming the normal distribution of the result using the Shapiro-Wilk test. Kaplan-Meier survival curves were plotted for the clinical survival of the groups and 95% confidence intervals (CI) were calculated. The log rank test was used as test of significance.

A p-value < 0.05 was deemed to be statistically significant. SPSS version 15.0 software (SPSS Inc., Chicago, Illinois) was used to analyse the data.

Results

The numbers of hips for which information on outcome was available for analysis at various periods of follow-up is presented in Table II while loss to follow-up and clinical failure are shown in Table III.

At a mean follow-up of four years (1 to 8), 364 hips (92.2%) had a satisfactory clinical result and had not required any surgery. Failure requiring THR occurred in 4 of 215 (2%) of Ficat stage-I hips, 10 of 129 (8%) of Ficat stage-II and in 17 of 51 (33%) of Ficat stage-III hips.

Kaplan-Meier survival analysis for the stages of avascular necrosis of the femoral head shown at presentation is given in Figure 1. Compared with Ficat stage-III hips, stage I- and stage-II hips showed a significantly higher probability of survival (log rank test, $p < 0.001$ for all associations).

The clinical outcome measures after treatment with alendronate are shown in Figure 2 and presented in Table IV. Other than in stage-III disease the mean scores remained significantly better than at presentation, long after discontinuation of treatment at three years.

The radiological progression is recorded in Table V and presented as a rate of collapse in Figure 3. At a mean follow-up of four years (1 to 8), the overall collapse rate was 28.8% (99 of 344 hips) in stage-I and stage-II hips taken together and 12.6% (27 of 215) in stage-I and 55.8% (72 of the 129) in stage-II hips. The mean time to collapse was 3.1 years (2 to 6) (3.5 years (3 to 6) for stage-I and 2.9 years (2 to 5) for stage-II hips). Radiological progres-

Table II. Number of hips available for analysis over eight years

Year of onset of treatment	Follow-up (yrs)							
	1	2	3	4	5	6	7	8
1999	45	45	45	44	42	40	37	32
2000	42	42	41	40	38	35	32	--
2001	50	50	49	48	46	44	--	--
2002	39	39	38	37	35	--	--	--
2003	46	46	45	44	--	--	--	--
2004	58	56	55	--	--	--	--	--
2005	65	63	--	--	--	--	--	--
2006	50	--	--	--	--	--	--	--
Number of hips analysed	395	341	273	213	161	119	69	32

Table III. Loss to follow-up and clinical failure at follow-up

	Follow-up period (yrs)							
	1	2	3	4	5	6	7	8
Loss to follow-up	3	4	4	6	4	4	5	*
Clinical failure	1	2	3	5	6	5	4	5

* the six-month period after follow-up due at eight years not yet reached

Fig. 1

Kaplan-Meier survival analysis showing hips with avascular necrosis of the femoral head grouped according to the Ficat and Arlet stage at onset of treatment.

sion was seen in 179 of 395 hips (45%) that included 99 of 215 (46%) hips in stage-I, 70 of 129 (54%) of stage-II hips and 10 of 51 (20%) of stage-III hips.

The analgesic requirement of all the patients who responded to alendronate (clinical survival) decreased gradually and the maximum duration was only two months after commencing treatment with alendronate. Mild dyspeptic symptoms were noticed in ten patients and headache and dizziness in six. These did not warrant the cessation of treatment and all resolved in less than a month. No other adverse effect was noted in any patient.

Discussion

A number of recent studies^{7,9,10,13} have successfully used bisphosphonates for the treatment of avascular necrosis of

the femoral head on the premise that the anti-resorptive and anti-inflammatory actions of this drug^{1,14,15} will counter the structural bone weakening caused by reparative osteocytic necrosis and apoptosis.^{16,17} However, all these studies were based on a short-term follow-up.^{7,9,10,13} There is experimental evidence that alendronate increases bone mineral density.¹⁸

Earlier studies of the natural history of avascular necrosis of the femoral head^{2,19-21} have reported an overall clinical rate of progression of 77% to 98% and a radiological progression rate of 68% to 75% at a mean follow-up of three years. In a review of 21 studies involving 819 hips followed for a mean of 34 months, only 22% were found to have a satisfactory clinical result following non-operative treatment, defined as no further need of surgical intervention.⁵ Of the 559 hips with radiological follow-up, 74% progressed radiologically. By contrast, in our study of 395 hips with a mean follow-up of four years following alendronate treatment, a satisfactory clinical result, defined as no surgical intervention, was seen in 92% of hips while radiological progression was seen in 179 of 395 hips (45%). Historical reports note a rate of collapse of the femoral head of 75% and 80% at two and four years, respectively, compared with our experience of 29% at four years. In untreated hips the conversion rate to THR was reported as > 50% at three years⁴ and 64% at two years.⁹ Recent studies have reported results according to the Ficat stage²² defining clinicoradiological failure as that used in our study. The proportions of hips requiring THR were 2%, 8% and 33% for staged-I, -II and -III disease respectively compared with 65%, 69% and 87% respectively as reported by Mont and Hungerford⁵ in untreated hips. Other reports categorising outcome according to the Ficat and Arlet grade at presen-

Fig. 2

Graphs showing the clinical outcome measures to a maximum of eight years after presentation. The results are separated into the avascular stages shown at the onset of treatment.

tation all describe worse results than we achieved in our patients who were treated with alendronate.²³⁻²⁸ This indicates a sustained action of alendronate in postponing surgical intervention and retarding the progression of collapse in all grades of avascular necrosis of the femoral head, but more marked in stage-I and stage-II disease. The length of follow-up of our study exceeded that of others²³⁻²⁸ allowing the conclusion to be drawn that alendronate given for three years maintains its benefits for up to eight years in some patients.

The natural history of untreated avascular necrosis of the femoral head based on MRI evaluation has recently been described.²⁹⁻³² The MRI-based Steinberg classification of avascular necrosis of the femoral head includes stages 0 to 3 which correspond to the pre-collapse Ficat grades I and II.²⁵ Survival rates ranging between 20% and 60% have been reported for Steinberg stage-1 to stage-3 hips at four to five years.^{27,28} Our experience at a mean duration of four years identified a combined rate of survival for Ficat stage-I and stage-II, of more than 90% (Fig. 1) confirming a favourable role of alendronate in earlier grades of avascular necrosis of the femoral head.

In the literature the general premise is that once collapse of the femoral head occurs, progression is relentless and that no conservative management is effective.^{5,28,33-38} Additionally, it has been reported that avascular necrosis as a diagnosis is a predisposing factor for early failure in THR or surface replacement.³⁹⁻⁴² Any medical management of this disease which at least defers the requirement for THR among these young patients with grade-III disease would be worthwhile.

The duration of alendronate therapy still needs to be optimised. Our results have shown that from three years onwards, there is a rapid deterioration of hips which were already at stage-III at the time of commencement of treatment. This suggests that in this advanced stage the process may be better controlled if the drug is continued for a longer period of time.

Our study started in 1998 and was limited by lack of access to routine MRI or the more recent quantitative digital image analysis,⁴³ which precluded the use of newer classification systems based on the site, size and progression of the lesion.⁴⁴ However, considering the large number of hips studied and the follow-up for some extending to eight

Table IV. Mean (SD) of clinical scores at various intervals (yrs) with statistical comparison with the score at presentation using the Wilcoxon signed-rank test

	At onset	Years									
		1	3 (alendronate stopped)				6	7		8	
Stage-I											
Pain score	4.5 (1.8)	1.5 (0.9)	p < 0.001	1.4 (0.9)	p < 0.001	1.8 (1.3)	p < 0.001	1.8 (1.0)	p < 0.001	1.8 (1.8)	p < 0.001
Disability score	5.1 (1.4)	1.7 (1.0)	p < 0.001	1.5 (0.9)	p < 0.001	1.9 (1.3)	p < 0.001	1.9 (1.1)	p < 0.001	1.9 (1.6)	p < 0.001
Standing time	16.3 (7.0)	59.2 (17.1)	p < 0.001	68.9 (24.3)	p < 0.001	67.5 (28.8)	p < 0.001	66.4 (25.3)	p < 0.001	71.8 (28.7)	p < 0.001
Walking time	13.7 (5.4)	44.8 (13.1)	p < 0.001	45.8 (15.3)	p < 0.001	45.0 (16.5)	p < 0.001	43.5 (17.4)	p < 0.001	46.8 (17.3)	p < 0.001
Stage-II											
Pain	5.1 (1.7)	1.6 (0.3)	p < 0.001	1.6 (0.9)	p < 0.001	2.3 (1.7)	p < 0.001	2.4 (1.7)	p < 0.001	3.0 (2.1)	p = 0.01
Disability score	5.3 (1.5)	1.8 (1.1)	p < 0.001	1.6 (0.8)	p < 0.001	2.5 (1.5)	p < 0.001	2.6 (1.7)	p < 0.001	3.0 (1.7)	p < 0.001
Standing time	14.7 (6.6)	54.1 (14.1)	p < 0.001	62.7 (28.9)	p < 0.001	50.6 (20.1)	p < 0.001	45.9 (25.0)	p < 0.001	45.4 (20.1)	p < 0.001
Walking time	13.4 (5.2)	43.2 (13.3)	p < 0.001	43.5 (14.4)	p < 0.001	36.8 (15.4)	p < 0.001	32.2 (17.8)	p < 0.001	31.5 (18.0)	p < 0.001
Stage-III											
Pain score	4.9 (1.7)	1.7 (1.2)	p < 0.001	2.0 (2.0)	p < 0.001	3.3 (2.0)	p < 0.001	4.8 (2.2)	p = 0.34	7.0 (0.0)	p = 0.32
Disability score	5.2 (1.4)	1.6 (1.1)	p < 0.001	1.9 (1.7)	p < 0.001	3.1 (2.1)	p < 0.001	4.3 (2.0)	p = 0.86	6.5 (0.7)	p = 0.18
Standing time	14.5 (6.3)	54.5 (11.6)	p < 0.001	58.4 (23.1)	p < 0.001	43.6 (20.6)	p < 0.001	37.1 (21.6)	p = 0.04	17.5 (3.5)	p = 1.00
Walking time	12.6 (4.7)	44.5 (12.1)	p < 0.001	42.0 (16.5)	p < 0.001	32.2 (15.7)	p < 0.001	27.9 (14.4)	p = 0.04	12.5 (3.5)	p = 0.32

Table V: The radiological status of the hips at follow-up

Follow-up duration (yrs)	Stage			
	I	II	III	IV
1 (n = 395)				
At onset	215	129	51	0
At last visit	214	120	61	0
2 (n = 341)				
At onset	179	117	45	0
At last visit	120	149	72	0
3 (n = 274)				
At onset	146	96	32	0
At last visit	73	110	90	1
4 (n = 213)				
At onset	112	77	24	0
At last visit	51	76	75	11
5 (n = 161)				
At onset	85	58	18	0
At last visit	38	48	63	12
6 (n = 109)				
At onset	59	39	11	0
At last visit	24	34	41	10
7 (n = 69)				
At onset	39	23	7	0
At last visit	13	26	21	9
8 (n = 32)				
At onset	17	13	2	0
At last visit	4	14	9	5

Fig. 3

Graph showing the percentage of collapsed hips over follow-up for eight years.

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Supplementary material

A further opinion showing a comparison of clinical and radiological fracture rates in treatment of avascular necrosis of the femoral head as seen in previous studies with those in our present study is available with the electronic version of this article on our website at www.jbjs.org.uk

years, the information obtained suggests that the natural history of avascular necrosis of the femoral head can be favourably altered by alendronate.

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