Efficacy of alendronate, a bisphosphonate, in the treatment of AVN of the hip. A prospective open-label study

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Objective. To study the efficacy of alendronate, in the treatment of avascular necrosis (AVN) of the hip.

Methods. Sixty patients with AVN of the hip (100 hips with AVN) were studied. The follow-up period ranged from 3 months to 5 yr. The most common cause of AVN was steroids. Parameters studied were walking time, standing time, pain and disability on a visual analogue scale (VAS), range of motion of the hip, X-ray and MRI of the hip. All patients were treated with alendronate 10 mg/day (or 70 mg/week) along with 500–1000 mg of daily calcium and vitamin D supplements, and were advised to avoid weight-bearing. NSAIDs and analgesics were permitted as needed and were recorded.

Results. Forty-one patients (71 AVN hips) with AVN have been followed up for a minimum of 1 yr, 24 patients (42 AVN hips) for 2 yr and 21 patients (37 AVN hips) for more than 2 yr (average 37 month). Fourteen patients have been followed up for less than 1 yr (3–9 months). Significant reduction in pain and disability scores ($P < 0.001$) and significant increase in standing and walking time ($P < 0.001$) were observed. All hip movements improved at 1 yr ($P$ value 0.000–0.009) with an insignificant decline after that ($P > 0.001$). Radiologically, the hips either stabilized in the same grade or progressed by one grade. MRI showed a decrease in marrow oedema in most cases at the 1-yr follow-up. Six patients (10 hips) required surgery and there were two (three hips) dropouts. The drug was well tolerated and there was a reduction in NSAID requirement.

Conclusion. Alendronate reduces pain, improves function and retards AVN progression. Early surgical intervention can be avoided in most patients.

Key words: Alendronate, AVN.

Avascular necrosis of the hip is a disabling and crippling disorder. Bone functions as a closed compartment. Under certain pathological conditions, such as trauma, steroid intake and haemostatic disorders, intra-osseous bone marrow pressure increases. This increased pressure is transmitted to small venules and capillaries within the bone, causing a decrease in blood flow to the bone, i.e. ischaemia.

Clinically AVN progresses through various stages [1]. Stages I and II are clinically asymptomatic though radiological changes are present. In stage III, there is intermittent pain, but the gait is normal. In stage IV, there is a sudden increase in pain, development of antalgic gait and limitation of hip movements. Stage V is characterized by intense pain and osteoarthritic changes of the hip, and in stage VI, the hip is severely degenerated with significant discomfort and impaired mobility. Most asymptomatic lesions progress from stage I or II to III within a period of 2 yr.

Its natural history is uncertain. There are various views, according to Merle d’Aubigne et al., who followed up 90 cases of AVN, collapse occurred in 20% within 1 yr and only 25% had escaped collapse 3 yr after the onset [2].

Arlet is of the view that there is involvement of both hips in 30–70% of cases at the time of first examination. Time elapsed between the diagnosis and severe deterioration of the joint, leading to a major surgical procedure, was about 3 yr in 50% of cases. There is still controversy about AVN e.g. are the early lesions localized to a conic arterial territory or are they dispersed throughout the proximal femur? Do the early lesions involve the marrow cells or osteocytes? When and why does the sequestrum appear? Can obliterator arteritis, either extra-osseous or intra-osseous, be demonstrated as one of the causes of bone ischaemia and necrosis? [3].

Non-surgical approaches to the treatment of AVN include protected weight-bearing, electrical stimulation (direct current, pulsed electromagnetic field or capacitative coupling) and pharmacological agents (vasodilators, lipid-lowering agents and anticoagulants). The outcome of non-surgical treatments has been less than ideal.

Several surgical procedures have been described to prevent femoral head collapse and progression of the disease. These include core decompression, osteotomies, non-vascularized bone grafting and vascularized grafts. Many studies have questioned the effectiveness of surgical procedures in early AVN [4]. The disease process progresses, ultimately leading to arthroplasty.

We have treated patients with AVN of the hip with alendronate, a bisphosphonate. It is an antiresorptive agent. It reduces the oedema and the rate of remodelling, thereby contracting the ‘remodelling spaces’ [5] and preventing the progression of bone collapse. The bone formed during alendronate treatment is histologically normal [6].

We have earlier reported our preliminary experience [7, 8]. In this communication, we report results of our experience on a larger number of patients followed up over a longer period of time.

Materials and methods

This was a prospective study. Between 1998 and October 2003, we treated 69 patients with AVN of the hip with alendronate.
Of these, six were excluded from the analysis because we were unable to follow them up regularly and another three did not come for follow-up after the first visit. Of the remaining 60 patients, 40 had bilateral AVN. In total there were 100 hips with AVN.

X-ray and MRI confirmed the diagnosis of AVN. A detailed history and findings were recorded on a pro forma. This included demographic data, history of trauma, alcohol and steroid consumption, duration of illness, walking time and standing time (in minutes), pain and disability on a visual analogue scale (VAS) and range of motion at the hip. In cases of steroid ingestion, the reason for this was also recorded. X-ray and MRI were graded according to Ficat and Arlet [9] and Mitchell et al. [10], respectively.

In Ficat’s classifications of AVN, stage 0 is preclinical and preradiographic. The diagnosis is suspected in one hip when the other hip has definite disease. This is the stage of truly ‘silent hip’. Stage I represents the earliest clinical manifestation of the syndrome. The patient complains of pain in the groin, which is worse at night. There is restricted abduction and internal rotation at the hip joint. Radiologically, there is subtle loss of clarity, with poor definition or blurring of the trabecular pattern and patchy osteoporosis. In stage II, there are radiographic changes in the trabecular pattern. Sclerosis may be diffuse, in localized areas, or in a linear arc which is concave superiorly. Decalcification is either generalized or in the form of small cysts. The mixed form includes both sclerosis and cysts. Stage III is characterized by the appearance of sequestrum on the radiographs. A crescentic line appears due to subchondral fracture, representing the transitional form between stages II and III. Joint space is preserved or increased. In stage IV there is progressive loss of articular cartilage and the development of acetabular osteophytes. The radiographic picture is that of osteoarthritis superimposed on a deformed femoral head.

In MR staging [10], AVN is diagnosed when a peripheral band of low signal intensity is present on all imaging sequences, typically in the superior portion of the femoral head, outlining a central area of marrow. This peripheral band is most apparent on T1-weighted sequences. On T2 sequences, the inner border of the peripheral band shows high signal in 80% of cases. This is called the ‘double line’ sign of AVN and is considered to be pathognomonic.

MR staging of the AVN is based on signal intensity of the centre of the marrow inside the dark line of necrosis. Often, several classes of signal intensity are present within the infarcted marrow. Unlike radiographic staging, MR classes have little predictive value regarding the prognosis for collapse of the femoral head. However, the MRI size and position of the AVN lesion is related to prognosis (D. A. Bluemke, Johns Hopkins Hospital; downloaded from the Internet).

MR staging is as follows: class A, bright on T1, intermediate on T2 (analogous to fat); class B, bright on T1 and T2 (analogous to blood); class C, intermediate on T1, bright on T2 (analogous to fluid); class D, dark on T1 and T2 (analogous to fibrous tissue). Some examples of MRI findings are shown in Figs 1–4.

All the patients were treated with alendronate 10 mg per day (or 70 mg once per week), given early in the morning on an empty stomach with two glassfuls of water. All patients received daily 500–1000 mg of calcium and 400–800 IU vitamin D₃. NSAIDs and analgesics were permitted as needed. All patients were advised to avoid weight-bearing (non-weight-bearing to toe touch, weight-bearing with elbow or axillary crutches). Patients were followed up every 3 months for the first year and every 6 months thereafter. At each visit, the above parameters and NSAID/analgesic requirement were recorded, as were side-effects or intolerance to alendronate, if any. X-rays were repeated at an interval of 3–6 months. MRI was repeated at an interval of 3 months up to 9 months or 1 yr and then yearly.

Statistical methods used were the $t$-test for paired samples for pain, disability, walking time, standing time and range of motion changes, and the $\chi^2$ test for X-ray changes. The study had local ethics committee approval. All the patients were informed about the study and that the drug was being used for the first time for the disease. Written consent was not insisted upon. Only those who consented were included in the study.
Results

Data for 60 patients (100 hips) about avascular necrosis of the hip were analysed (Fig. 5). There were 42 male patients. The age range was 18–70 yr. The duration of AVN before instituting alendronate was 0–36 months. The follow-up was less than 1 yr for 20 hips. Their data were not analysed. So far, 41 patients (71 hips) have been followed up for 1 yr, 24 patients (42 hips) for 2 yr and 21 patients (37 hips) for more than 2 yr (average 37 months). The maximum follow-up was 5 yr. The cause of AVN was steroids in 28 patients. The underlying diseases needing steroids were SLE (10 patients), psoriasis and other skin diseases (five), interstitial lung disease (two), rheumatoid disease (one), asthma (four), renal transplant (one), carcinoma (four), sarcoidosis (one). Alcohol (12), idiopathic (six), trauma (five), multiple factors (alcohol, trauma, smoking) (seven), postpartum (one) and smoking (one) accounted for the rest.

Figure 5 depicts the follow-up data of all patients. At the end of 1 yr, two patients had dropped out and three patients (five hips) needed arthroplasty. At the end of 2 yr, there were no dropouts but three more patients (five hips) needed arthroplasty. Among the dropouts, one had bilateral grade 4 AVN and the other had grade 2 AVN. There were no dropouts in patients followed over 2 yr and no surgeries were needed (Table 1).

At all points of time, there was significant improvement in all clinical parameters, [walking time, standing time, pain and disability (P < 0.001)] except range of motion (Table 2), which, after improvement in the first year (P = 0.000–0.009), showed a small deterioration (statistically not significant, \( P = -0.012 \) to 0.918) in all movements except flexion, which continued to improve. Mean changes in pain, disability, walking time and standing time at follow up were as follows. Between 0 and 1 yr (41 patients): pain (VAS), 6.0 (s.d. 2.3) became 2.2 (s.d. 1.8); disability (VAS), 5.2 (s.d. 2.4) became 2.3 (s.d. 1.8); standing time, 19 min (s.d. 15) became 45 min (s.d. 19); walking time, 16 min (s.d. 15) became 41 min (s.d. 20). Between 0 and 2 yr (24 patients): pain (VAS), 6.1 (s.d. 2.6) became 1.6 (s.d. 1.5); disability (VAS), 4.9 (s.d. 2.3) became 1.7 (s.d. 1.4); standing time, 18 min (s.d. 15) became 51 min (s.d. 19); walking time, 16 min (s.d. 15) became 46 min (s.d. 21). Between 0 and 2+ yr (21 patients): pain (VAS), 6.6 (s.d. 2.5) became 2.0 (s.d. 2); disability (VAS), 4.8 (s.d. 1.9) became 2.4 (s.d. 2); standing time, 14 min (s.d. 9.7) became 45 min (s.d. 26.5); walking time, 12 min (s.d. 10) became 37 min (s.d. 26).
X-ray grades of the hips with AVN are shown in Table 3. Radiologically (Table 4), deterioration by one grade was seen in 10 out of 71 hips in the 1-yr group, 11 out of 42 hips in the 2-yr group and 16 out of 37 hips in the group with follow-up greater than 2 yr. Deterioration by two grades was seen in one and four cases in the 2-yr and 2+ yr follow-up groups, respectively. Thus, radiological deterioration was seen in 14% at 1 yr, 28% at 2 yr and 54% in the group with more than 2-yr of follow-up. Radiological stabilization in two cases is shown in Figs 6a–c and 7a–d. MRI showed resolution of oedema in 3–6 months (Fig. 6d–f).
Discussion

AVN of the bone is a chronic progressive disorder with significant morbidity. It is characterized pathologically by bone marrow ischaemia with eventual death of bone trabeculae. As bone repair occurs, the mechanically weak bone collapses due to weight-bearing.

The natural history of AVN is variable, but in most patients there is early collapse of bone, leading ultimately to joint destruction necessitating arthroplasty. This has been reported to occur within 4 yr of diagnosis in at least 80% of cases [11]. It has also been suggested that more than half of the hips will undergo total hip replacement within 3 yr [12]. In an attempt to prevent progressive bone collapse and joint damage, a variety of surgical approaches, such as core decompression, bone grafting and osteotomy, have been tried with variable success.

Even in the short term, results of core decompression vary greatly: Ficat [9] reported 89.5% success for the pre-collapse stage while Camp and Colwell reported a 40% success rate [13]. The results of vascularized fibular graft from different centres

Fig. 6. Serial X-rays and MRI, case 1. (a) Baseline X-ray at the time of starting alendronate. Grade 2 AVN on the right side with lytic lesion in the femoral head. (b) Two-year follow-up. The joint space and head contour have been maintained; the lytic lesion has regressed minimally. (c) Three years. There is no collapse and AVN has stabilized. (d) MRI showing marrow oedema and joint effusion on the right side. (e) Decreased marrow oedema and joint effusion after 3 months of alendronate treatment. (f) No marrow oedema, and the femoral head contour has been maintained at 32 months.
have also varied, with success rates ranging from 60 to 90% at short follow-up (less than 3 yr) [14]. Thus, the results of surgery for early AVN with a view to arrest or slowing of progressive bone and joint damage are at best equivocal. Furthermore, there is the associated surgical morbidity. There is, therefore, a need to explore alternative surgical and non-surgical approaches. We have used alendronate, a bisphosphonate, to treat AVN of the hip. We have included patients at all stages of AVN in a prospective open-label study. Since there are no previous data on this subject, no comparative placebo group was studied. This was thus a preliminary study to assess the efficacy of alendronate in the treatment of AVN of the hip. Bisphosphonates are antiresorptive agents that act by inhibiting the action of mature osteoclasts on bone. Bisphosphonates appear to stimulate transiently the proliferation of pro-osteoblast cells and increase their differentiation, increase the production of antiresorptive protein osteoprotegerin by osteoblasts [15] and decrease oedema at the site of AVN, possibly through their anti-inflammatory action [16]. Antiresorptive agents reduce the rate of bone remodelling, thereby contracting the remodelling spaces. Under their influence, although the slower remodelling imperceptibly reduces bone tissue, the remaining bone tissue becomes more mineralized and thus denser. The slowly decreasing tissue mass thus becomes more densely laden with minerals and is better able to withstand the stress of weight-bearing [5]. Bisphophonates thus seem to preserve bone architecture and also to increase bone mineral density.

The progressive collapse of ischaemic bone is the result of a reparative process in which there is resorption of necrotic bone by osteoclasts. It appears logical to postulate that if the action of osteoclasts can be inhibited (by bisphosphonates), resorption and progressive collapse of bone could be reduced, if not halted. There is experimental evidence to support this postulate. In a bone chamber study in rats [17], to test whether resorption of necrotic
bone can be prevented, structural grafts were subjected to new bone ingrowth during systemic bisphosphonate treatment. The experimental study showed that systemically administered alendronate prevented resorption of necrotic bone during revascularization. This experimental study was done with the background knowledge that structural failure and subsequent joint dysfunction and pain in avascular necrosis is the result of resorption of necrotic bone during revascularization, before

FIG. 7. Serial X rays, case 2. (a) Baseline X-ray. There is bilateral grade 2 AVN with lytic lesions in the femoral head on both sides. (b) X-ray at 1 yr. Sclerosis is regressing. (c) Two years of follow-up. Joint space and head contour have been maintained. There is no progression of AVN. (d) Three years. AVN is still grade 2. Changes have remained static since the second year.
new bone has formed or consolidated enough for load-bearing. Bone resorption can be reduced by bisphosphonates. If the resorption of the necrotic bone could be reduced during the revascularization phase until sufficient new bone has formed, it would appear that structural failure could be avoided. Evans et al. [18] studied the effect of alendronate in osteogenesis imperfecta in an oim mouse model. Their results indicate that high doses of alendronate inhibit long bone length in mice through alteration of the growth plate and possibly reduced resorption of the chondro-osseous junction.

Based on above postulates and facts, bisphosphonates have been used successfully to treat osteogenesis imperfecta [19] and Gaucher’s disease [20–22]. AVN seems an ideal indication for treatment with bisphosphonates.

Our experience shows that alendronate is very effective in stages I and II and early stage III of AVN. It decreases pain and disability within a few weeks, and also retards progressive bone collapse. It thus seems to favourably alter the natural history of AVN. If one extrapolates the published data on the natural history of AVN to our patient group of 100 hips, in 3–4 yr 50–80 hips would have needed surgery, but in effect only 10 hips needed surgical intervention. Out of these 10, eight were already advanced cases (stages III and IV) when started on alendronate.

Pain relief is probably the result of decreased bone oedema, as seen in MRI changes. Range of motion showed improvement initially, possibly by reduction of bone oedema and joint effusion, and then showed a gradual though insignificant decrease. Radiologically, the disease did progress but not significantly. These results indicate that alendronate is not a cure; it only slows down the progression of AVN. The number of the hips undergoing surgery at 1 yr (6.32%), 2 yr (18.2%) and at longer follow-up (average at 37 months, 20%) is comparable and even better than the result of the core decompression and fibular graft [13, 14], as already stated.

The trial was started with the intention of studying the effect of an antiresorptive agent in AVN with sufficient support from the literature for the use of these agents to reduce the rate of remodelling. This is an ongoing study, and as more and more patients enter long-term follow-up, more definitive data are likely to emerge. At present it is not clear how long to continue alendronate.

We envisage double-blind placebo-controlled studies on larger numbers of patients, and the use of other antiresorptive agents.

The main advantage of treatment with alendronate is that it is a safe drug, gives early relief from pain with a reduced requirement for NSAIDs (with a decrease in drug-induced morbidity) and, more importantly, postponement of the need for surgery.

The authors have declared no conflicts of interest.

## References