Clinical and Radiological Amelioration of Refractory Peripheral Spondyloarthritis by Pulse Intravenous Pamidronate Therapy

WALTER P. MAKSYMOWYCH, ROBERT LAMBERT, GIAN S. JHANGRI, SHARON LECLERCQ, PETER CHIU, BEN WONG, STEPHEN AARON, and ANTHONY S. RUSSELL

ABSTRACT. ***Objective***. To examine the potential therapeutic properties of an aminobisphosphonate, pamidronate, using clinical and laboratory outcome variables together with dynamic magnetic resonance imaging (MRI) and gadolinium augmentation in patients with spondyloarthropathy (SpA) refractory to nonsteroidal antiinflammatory drugs (NSAID).

Methods. We studied 9 patients (7 male, 2 female) of mean age 27.9 years (range 19–38) and mean disease duration of 5.5 years (range 0.5–20). Five had ankylosing spondylitis (AS), 3 had undifferentiated SpA, and one had reactive arthritis. Seven were HLA-B27 positive. Two had inflammatory bowel disease. Pamidronate (60 mg) was given intravenously on Days 1, 2, 14, 28, and 56, over 4 h in 500 ml of 5% dextrose. Clinical outcome assessments included the BASDAI (disease activity), BASFI (function), BASGI (global well being) composite visual analog instruments, and swollen and tender joint count. Laboratory variables included the erthrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Dynamic MRI with gadolinium augmentation of synovium and bone was performed at baseline and at Day 84 in the first 6 patients enrolled in the study.

Results. All patients completed the study and there was a significant improvement in all clinical and laboratory variables assessed. Mean swollen and tender joint count decreased by 93.8% ($p = 0.017$) and 98.2% ($p = 0.012$), respectively, and complete clinical resolution of synovitis was noted in 5 patients. BASDAI decreased by 44.2% ($p = 0.028$), BASFI by 47.3% ($p = 0.015$), and BASGI by 42.2% ($p = 0.011$). ESR and CRP declined by 49.4% ($p = 0.012$) and 66.9% ($p = 0.008$), respectively. Acute lymphopenia accompanied by elevated CRP levels was noted in 8 patients in the 48 h after first pamidronate infusion. Maximal rate and magnitude of enhanced MRI signal after gadolinium augmentation decreased after pamidronate therapy, especially in the bone marrow.

Conclusion. Preliminary data from uncontrolled studies support the efficacy of pamidronate therapy for NSAID refractory SpA and warrant further evaluation in controlled trials. (J Rheumatol 2001;28:144–55)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS
PAMIDRONATE
TREATMENT
MAGNETIC RESONANCE IMAGING

The treatment of spondyloarthropathy (SpA) has undergone little change since the advent of nonsteroidal antiinflammatory agents (NSAID). There is no evidence that these agents influence the underlying course of disease and they are associated with significant gastric and enteric toxicity[1,2]. Further, it has been estimated that at least 25% of patients may be NSAID refractory and this has been associated with a poor longterm outcome[3]. A number of studies have examined sulfasalazine (Salazopyrin) in SpA and reported variable results. Two large multicenter trials have been consistent in demonstrating lack of efficacy for this agent, with the exception of that subgroup of patients with SpA with polyarticular peripheral joint involvement[4,5]. However, even in this subgroup the beneficial effects were small and of doubtful clinical value, the mean improvement in visual analog score for pain being 16% compared to baseline. Further, life table analysis has shown that by 2 years at least 60% of patients have discontinued sulfasalazine therapy, largely because of lack of efficacy[6].

Reappraisal of the histopathology of early disease and of magnetic resonance imaging (MRI) has prompted us to examine an alternative approach. Evidence has accumulated that bone marrow inflammation, particularly in subchondral marrow of the iliac portion of the sacroiliac joint[7] and adja-

From the Departments of Medicine, Radiology, and Public Health Sciences, University of Alberta, Edmonton, Alberta, Canada.

Dr. Maksymowych is a scholar of the Alberta Heritage Foundation for Medical Research.

W. Maksymowych, FRCPC, Department of Medicine; R. Lambert, FRCPC, Department of Radiology; G.S. Jhangri, MSc, Department of Public Health Sciences; S. LeClercq, FRCPC; P. Chiu, FRCPC, Department of Medicine; B. Wong, MD, Department of Radiology; S. Aaron, FRCPC, Department of Medicine; A.S. Russell, FRCPC, Department of Medicine.

Address reprint requests to Dr. W. Maksymowych, 562 Heritage Medical Research Centre, University of Alberta, Edmonton, Alberta T6G 2S2.

Submitted May 12, 2000 revision accepted August 24, 2000.

cent to para and intraarticular entheseal attachments[8], is an important pathologically evident lesion in SpA. In the case of the sacroiliac joint, it is perhaps the earliest one[9]. Bisphosphonates not only selectively localize to bone but may also possess antiinflammatory properties. These include dose dependent inhibition of antigen presentation[10] and cytokine generation *in vitro*[11] and suppression of both antigen and adjuvant induced arthritis in animal models[12,13]. There are a limited number of reports examining the potential antiinflammatory properties of pamidronate, an aminobisphosphonate, in patients with rheumatoid arthritis[14-16]. Variable dosage, routes of administration, and dosing regimes have been employed and consequently the variable outcome data are not surprising.

Until recently the examination of novel therapeutic approaches in SpA was hampered by the lack of internationally validated outcome instruments. More recently this issue has been addressed through the development and general validation of instruments that measure disease activity, functional change, and global improvement[17-19]. However, validation has been primarily conducted in the context of a physiotherapeutic rather than pharmacologic intervention. Other workers have shown that dynamic MRI (dMRI) with gadolinium augmentation can be used to assess not only the degree of inflammation within a particular joint but also the response to therapeutic intervention[20,21]. Gadolinium accumulates at sites of increased capillary permeability. The rate and degree of accumulation reflects the degree of inflammation and can be documented by dMRI[22]. Criteria have been developed to quantify the severity of inflammation within the sacroiliac joint[23] and others have validated this approach by evaluating the effects of intraarticular steroid injection into the sacroiliac joints of patients with SpA[24].

In a preliminary report, we showed that the intravenous (iv) administration of pamidronate, given monthly for 6 months, was associated with symptomatic improvement in a group of patients with longstanding, primarily axial AS accompanied by a significant decrease in the erythrocyte sedimentation rate (ESR)[25]. Pamidronate was also noted to induce lymphopenia within 48 h of administration, which normalized over 1–2 weeks. This has been documented, and could be associated with immunomodulatory properties[26,27]. We have since examined this approach in a group of patients with active peripheral SpA refractory to NSAID as well as, usually, to intraarticular steroids and second-line drugs. Since currently available outcome instruments have not been comprehensively validated with respect to pharmacological interventions, we also evaluated the therapeutic response to pamidronate using dMRI. Furthermore, since the antiinflammatory properties of bisphosphonates appear to be dose dependent and may be related to their ability to induce short lived lymphopenia, we employed a schedule of iv administration for these patients with refractory peripheral joint disease that was both more intensive and over a more limited time period than used in our earlier report[25].

MATERIALS AND METHODS

Patients. In this pilot study, we examined 9 consecutive patients (7 male, 2 female) of average age 27.9 years (range 19–38) and mean disease duration of 5.5 years (range 0.5–20) (Table 1). Five fulfilled the modified New York criteria for ankylosing spondylitis (AS), 3 were diagnosed with undifferentiated SpA, and one with reactive seronegative arthritis. Preceding *Campylobacter jejuni* enteritis was documented in this latter patient. Two patients with AS had concomitant inflammatory bowel disease and no patient had psoriasis. Seven were HLA-B27 positive. All had persistently active peripheral synovitis despite therapy with NSAID. All patients with knee synovitis and the one patient with hip disease had also previously received an intraarticular steroid injection and were currently receiving or had previously received second-line agents (sulfasalazine up to 3 g/day, methotrexate up to 30 mg weekly intramuscularly). NSAID therapy had been stable for at least one month and second-line therapy for 3 months prior to study entry. Intraarticular steroids were not permitted for 2 months prior to study entry and for the duration of the study. Concomitant stable therapy at study entry was maintained at constant dosage levels for the duration of the study.

Three patients had active synovitis of the knee joints only (one unilateral, 2 bilateral). Two had active midfoot involvement only, evident clinically and on bone scan (data not shown). One had active hip disease only, evident clinically and on bone scan (data not shown), and 3 had polyarticular involvement.

Study protocol. Sixty milligrams of pamidronate was administered iv in 500 cc of 5% dextrose over 4 h on Days 1, 2, 14, 28, and 56. Outcome assessments were performed at baseline and at Day 84.

Table 1. Clinical characteristics of study patients at baseline.

Patient	Age	Sex	Diagnosis	Disease Duration	Active Joints	Therapy	HLA-B27
1	38	M	USpA	7 mo	Knees, ankles	Indomethacin	No
2	32	M	AS/UC	5 yrs	Elbow, knee	Etodolac	No
3	37	F	AS	20 yrs	Mid-foot	Diclofenac, SSZ, MTX	Yes
4	21	M	USpA	6 mo	Knee	Diclofenac	Yes
5	22	F	Reactive arthritis *(Campylobacter)*	1 yr	Elbow, wrists, knees, Ankles, PIP	MTX, SSZ Diclofenac	Yes
6	19	M	USpA	6 mo	Knees	Diclofenac	Yes
7	34	M	AS, Crohn's	16 yrs	Knees	Diclofenac, MTX	Yes
8	19	M	AS	3 yrs	Hip	Diclofenac, SSZ	Yes
9	29	M	AS	3 yrs	Mid-foot	Indomethacin	Yes

SSZ: sulfasalazine; MTX: methotrexate; UC: ulcerative colitis; USpA: undifferentiated spondyloarthropathy; PIP: proximal interphalangeal joints.

Clinical outcome assessments. Clinical assessments included the Bath Ankylosing Spondylitis Disease Activity index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and Bath Ankylosing Spondylitis Global Index (BASGI) questionnaires, which have been previously validated. A swollen and tender joint count was performed.

Laboratory outcome assessments. Laboratory assessments included the ESR, C-reactive protein (CRP), and complete blood count, which were performed at baseline and for 2 consecutive days after first infusion. ESR and CRP were repeated on Day 84.

Magnetic resonance imaging. Unilateral scans were performed on all joints with a surface coil using a Phillips 1.5 Tesla machine. All sequences were performed with: (a) 180 mm field of view (FOV) (except hip joint 200 mm FOV); (b) 256 × 204 matrix (except dynamic sequence 256 × 256 matrix); (c) 4 mm slice thickness (except dynamic sequence 6 mm slice thickness); (d) 4 signal averages. All patients had a minimum of 4 types of sequence: T1 spin echo (SE), T2 turbo spin echo (TSE), short tau inversion recovery (STIR), and dynamic MRI with gadolinium augmentation (dMRI).

After acquisition, all dMRI sequences were subtracted [subtracted dynamic MRI with gadolinium augmentation (sdMRI)].

The dynamic augment sequence (dMRI) was performed with a limited number of slices in a single 2-dimensional plane — in this study, 4 slices in the coronal plane. Image acquisition must be fast and a T1 weighted gradient echo sequence was employed with a short TR (50 ms), short TE (12 ms), and wide flip angle (70º). Each series of 4 images took 26 s to acquire. The first series was acquired before augmentation. Gadolinium was injected during the 26 s of the second series and 10 subsequent series were acquired at 26 s intervals. The resultant images reveal the distribution of augmentation. Maximal rate (speed) and magnitude of augmentation can be calculated for any area. After the dMRI is completed, the first series can be subtracted from all other dMRI series, resulting in subtracted images (subtracted dynamic MRI with gadolinium augmentation — sdMRI). This highlights the visual effect of the augmentation.

Patients returned for followup MRI at Day 84. Every effort was made to ensure reproduction of position of patient and surface coil. Multiple scout images were acquired until the precise location of the pretreatment sequences could be reproduced.

Numerical data were retrieved by first identifying focal or diffuse areas of augmentation within synovium and bone marrow on the twelfth series of the pretreatment sdMRI image. Using the non-subtracted dMRI image, regions of interest were drawn and then reproduced in an identical location for all 12 images, and also in the same location for posttreatment MRI. For each region, mean signal intensity [magnitude of the vector in units of signal intensity (SI) per pixel] and standard deviation were recorded. Data were analyzed comparing the maximal rate and magnitude of augmentation between pre and posttreatment dMRI. The rate of dynamic augmentation was determined by calculating the percentage increase in SI between each consecutive series according to the following equation:

rate of augmentation (% increase per s) = $(SI_{T2} - SI_{T1}) \times 100 / (SI_{baseline} \times T)$, where T represents the time interval (26 s) between 2 consecutive series of images, corresponding to SI_{T2} and SI_{T1}, and $SI_{baseline}$ represents the signal intensity at baseline. The maximal value for rate of augmentation in the pretreatment series was then compared with the posttreatment value. The magnitude of augmentation or maximum signal intensity (SI_{max}) was arbitrarily designated as the value at a time point (T_{max}) beyond which further increases in SI were less than 5%.

A radiologist otherwise unconnected with this study visually assessed STIR sequences in a random, blinded manner for presence and severity of joint effusion, enthesopathy, bone erosion, focal bone marrow edema, and diffuse bone marrow edema.

Statistics. The nonparametric Wilcoxon signed rank test was used to examine the significance of changes observed after treatment in comparison to baseline values. A value of $p < 0.05$ was considered significant.

RESULTS

All patients completed the study and there was a significant improvement in all clinical and laboratory variables assessed. Diminution of synovitis was generally observed after the fourth infusion of pamidronate (i.e., after Day 28). The mean disease activity score (BASDAI) decreased by 44.2% (p = 0.028), the mean functional score (BASFI) by 47.3% (p = 0.015), and the global score (BASGI) by 42.2% (p = 0.011) (Table 2). This was accompanied by significant reductions in swollen (93.8%; p = 0.017) and tender joint (98.2%; p = 0.011) counts, with complete clinical resolution of synovitis in 5 of the 9 patients (Patients 1, 3, 4, 6, and 7) and partial improvement in 3 additional patients (Patients 2, 5, and 8). A significant reduction of 49.4% (p = 0.012) and 66.9% (p = 0.008) in ESR and CRP, respectively, was also noted. Although there was no significant change in outcome assessments in the patient with hip involvement (Patient 8), this patient reported a significant diminution in nocturnal

Table 2. Clinical outcome measures at baseline and at 3 months in SpA patients who received pulse iv pamidronate therapy.

Score	Baseline Mean ± SD	3 Mo Mean ± SD	p[a]
BASDAI	5.31 ± 2.43	2.68 ± 1.55	0.028
Morning stiffness[b]	5.77 ± 3.46	2.70 ± 2.10	0.038
Peripheral joint pain[c]	5.23 ± 3.10	2.48 ± 1.28	0.024
BASFI	4.73 ± 2.38	2.73 ± 2.17	0.015
BASGI	6.74 ± 2.17	3.92 ± 2.01	0.011
Swollen joints	4.33 ± 4.85	0.44 ± 1.01	0.012
Tender joints	3.78 ± 4.24	0.22 ± 0.67	0.008
ESR	29.89 ± 18.13	14.44 ± 12.41	0.017
CRP	43.90 ± 45.88	10.60 ± 10.39	0.012

[a] Wilcoxon signed rank test.
[b] The mean value for summated items 5 and 6 of the 6-item BASDAI questionnaire measuring the quality and duration of morning stiffness, respectively.
[c] The mean value for item 3 of the BASDAI questionnaire measuring the degree of pain/swelling in peripheral joints.

pain. In addition, a 21.7% reduction in hip pain by visual analog score (BASDAI component) was noted, accompanied by a decrease in ESR from 19 to 8 mm/h and CRP from 11 to 4.3 mg/l.

Lymphopenia (mean reduction of 57.9%; range 22.2 to 86.7%) was noted in 8 of the 9 patients by the second day after the first pamidronate infusion and was accompanied by a mean increase in CRP of 58.5 mg/l (range 6.6–135.6 mg/l) from baseline values. Changes in lymphocyte count and CRP were not observed in the patient presenting with hip disease (Patient 8).

MRI was performed on 6 patients and the presence and severity of effusion, enthesopathy, bone erosion, focal bone marrow edema, and diffuse bone marrow edema were assessed on T2 weighted STIR sequences (Table 3). Focal and diffuse bone marrow edema present on baseline MRI improved in all patients. Evidence of focal bone erosion at the medial edge of the tibial plateau in Patient 6 improved dramatically. Five patients had joint effusion at baseline, with improvement or resolution in 4 after therapy (all except Patient 8). In 2 patients (5 and 8), well defined areas of bone marrow edema/soft tissue inflammation at sites of tendon or ligament insertion were consistent with enthesopathy. Abnormal signal in Patient 5 improved after treatment.

Maximal rate and magnitude of synovial gadolinium augmentation at baseline and at Day 84 after the start of pamidronate therapy was determined by analyzing regions of interest within identical areas of synovium on dMRI. A total of 7 joints from the first 6 individuals entered into the study were examined, including 5 knees, 1 hip, and 1 midfoot (Patients 3, 4, 5, 6, 7, and 8). Both knees were examined in one patient with bilateral knee synovitis (Patient 7), and values for the knee joint in one patient (Patient 4) represented a mean of data from 3 regions of interest. This analysis was repeated for bone marrow. Only 3 patients had significant augmentation within bone on baseline images (Patients 3, 6, and 8). Two regions of interest, within acetabulum and femoral head, were examined in the one patient with hip joint involvement (Patient 8). An example of the effects of pamidronate on the dynamics of gadolinium augmentation in knee joint synovium of Patient 4 is provided in Figure 1. Treatment is followed by a decrease in maximal rate and magnitude of augmentation.

Decreased maximal rate and magnitude of synovial augmentation following pamidronate therapy was observed in all joints examined, with the exception of the individual with hip joint disease (Figure 2). The mean reductions of 38.5% and 42.3% in the maximal rate and magnitude of augmentation, respectively, in the 5 knee joints examined were consistent with clinical amelioration of synovitis. The greatest reductions after pamidronate therapy were observed in regions of interest within bone, the reductions being noted in all regions of interest showing augmentation at baseline (mean reduction of 76.3% and 80.7% in maximal rate and magnitude of augmentation, respectively) (Figure 3). Patient 4 had knee joint synovitis and experienced complete clinical remission during pamidronate therapy, maintained upon patient initiated discontinuation of NSAID therapy 6 weeks into the study, which was reflected by marked decrease in gadolinium augmentation on MR imaging (Figure 4).

Particularly striking reduction in gadolinium augmentation was noted in the acetabulum and femoral head of the patient with hip joint disease, despite the increased rate of synovial augmentation (Figure 5). One patient with clinical and bone scan evidence of midfoot involvement (Patient 3) was noted to have augmentation of the medial tendon sheaths, surrounding the peroneus longus tendon, and in the cuboid bone on baseline MRI, which also decreased after pamidronate therapy (Figure 6).

Seven of 9 patients experienced transient arthralgias and myalgias within 48 h of the first infusion of pamidronate that resolved over the ensuing 48 h. One of the 2 patients who did not experience this reaction (Patient 8) was also the only patient in whom lymphopenia and elevated CRP levels were not observed following the first infusion of pamidronate. There were no additional adverse events.

Patients have been followed posttreatment for a mean duration of 11.2 months (range 5–14). Six have had no recurrence of synovitis in joints affected prior to

Table 3. Presence and extent of disease before and after pulse iv pamidronate therapy as examined by MRI STIR sequences.

Patient	Effusion		Enthesopathy or Bone Erosion		Focal Bone Marrow Edema		Diffuse Bone Marrow Edema	
	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx	Pre-Rx	Post-Rx
3	–	–	–	–	+++	+	++	+
4	++	–	–	–	–	–	+	–
5	+	–	++	+	+++	++	++	+
6	++	+	++	+	++	–	+	–
7	+++	+	–	–	–	–	–	–
8	+	++	++	++	+++	++	+++	+

–: absence of symptoms; +: xxx; ++: xxx; +++: xxx.

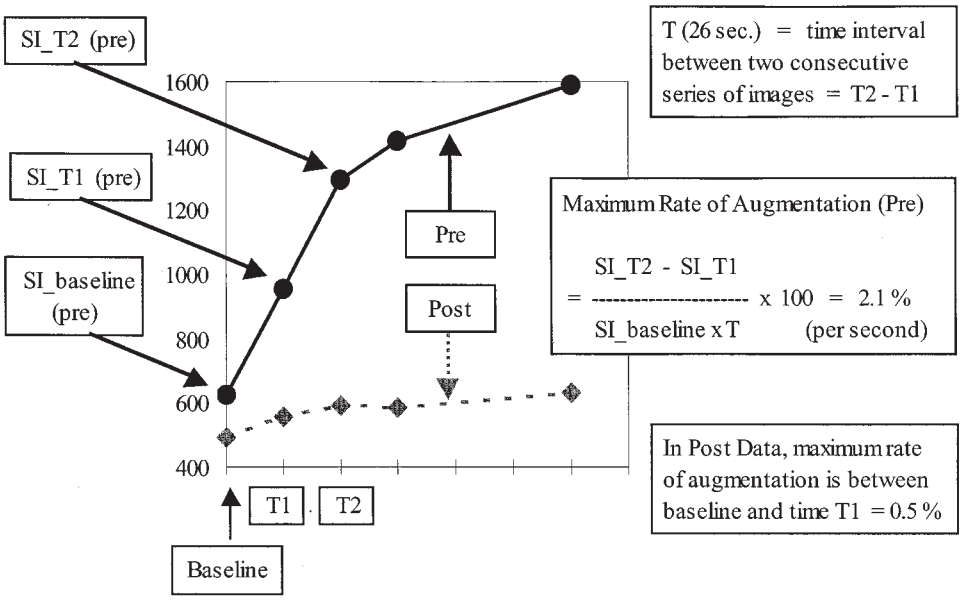


Figure 1. Effects of pulse intravenous pamidronate (60 mg per infusion) given on Days 1, 2, 14, 28, and 56, on the dynamics of gadolinium augmentation in the knee synovium of Patient 4.

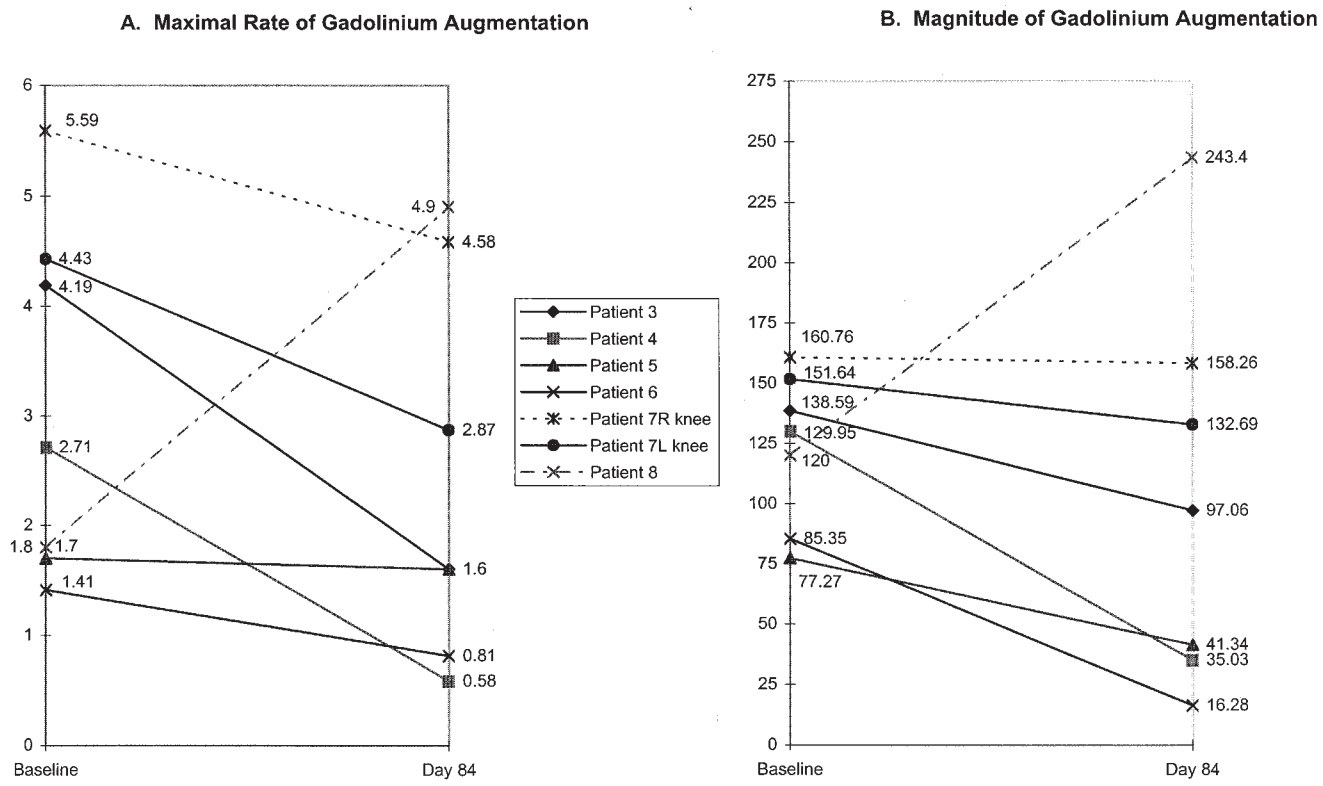


Figure 2. Effects of pulse intravenous pamidronate (60 mg per infusion), given on Days 1, 2, 14, 28, and 56, on the maximal rate (A) and magnitude (B) of gadolinium augmentation within synovium determined following dynamic MRI.

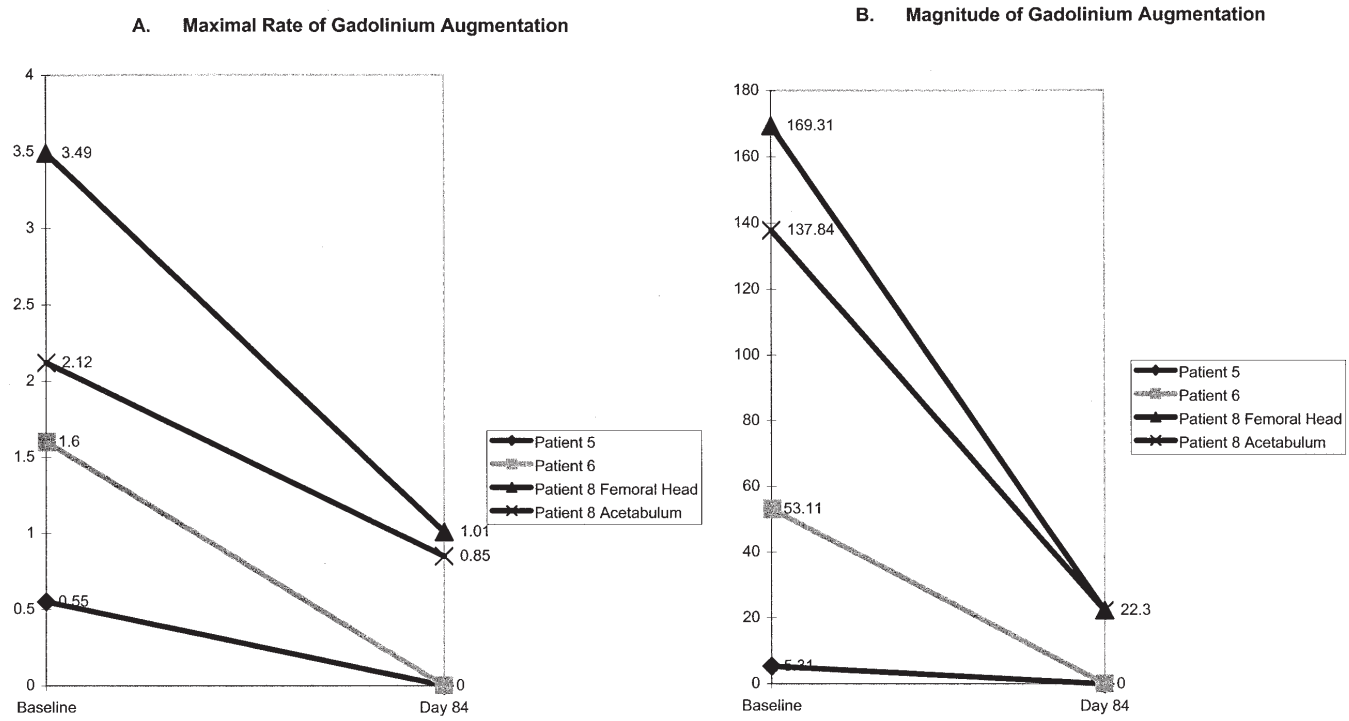


Figure 3. Effects of intravenous pamidronate (60 mg per infusion), given on Days 1, 2, 14, 28, and 56, on the maximal rate (A) and magnitude (B) of gadolinium augmentation within bone determined following dynamic MRI.

pamidronate therapy. One patient (Patient 5) was able to discontinue NSAID and second-line therapy 4 months after pamidronate therapy and has been in remission for the past 8 months although requiring surgery for joint contractures. Patients 4 and 7 experienced a recurrence of synovitis in the knees 4–6 months posttreatment. Intraarticular corticosteroid injections were administered into the affected knee joints. Responses were partial and of short duration (3 weeks). Both patients gave consent to repeat courses of pamidronate therapy. Retreatment with the same course of pamidronate induced remission of synovitis as before.

DISCUSSION

The clinical and radiological outcome variables examined in this open analysis of pulse iv pamidronate therapy appear to show efficacy for this therapeutic approach in patients with refractory peripheral SpA. The treatment was well tolerated and followup suggests that some patients may experience durable remissions and that those who relapse may respond to retreatment.

Despite inherent limitations of any open study, it is noteworthy that all patients given pamidronate had active ongoing synovitis despite therapy with NSAID. Most had also received intraarticular steroids and were either receiving or had already received second-line agents (sulfasalazine and/or methotrexate). Although spontaneous resolution of peripheral synovitis is widely recognized in patients with SpA, it is noteworthy that one patient with bilateral knee and another with midfoot involvement had both had persistent disease for several years, despite requiring methotrexate in doses of up to 30 mg weekly in the former patient. Clinical resolution of synovitis was evident by 2 months in this patient, permitting dosage reduction to 15 mg of methotrexate weekly posttreatment. A gradual recurrence of knee synovitis necessitated a repeat course of therapy 6 months later after an inadequate response to intraarticular steroid. Clinical resolution of synovitis was again documented (data not shown). The one patient with refractory hip joint synovitis experienced persistent effusion and an apparent increased rate of gadolinium augmentation within synovium posttreatment. In contrast, a marked reduction in the rate and magnitude of augmentation within the acetabulum and femoral head was noted after therapy. A number of possibilities may account for this discrepancy. First, as the patient was more comfortable at the time of the second scan, the femur was slightly more extended and externally rotated during the MRI. The different position may have resulted in a sampling error. Alternatively, since the antiinflammatory effects of pamidronate seen *in vitro* appear to be dose dependent, localization of drug to sites of active bone turnover will result in relatively higher local concentrations within bone than in synovium. This could

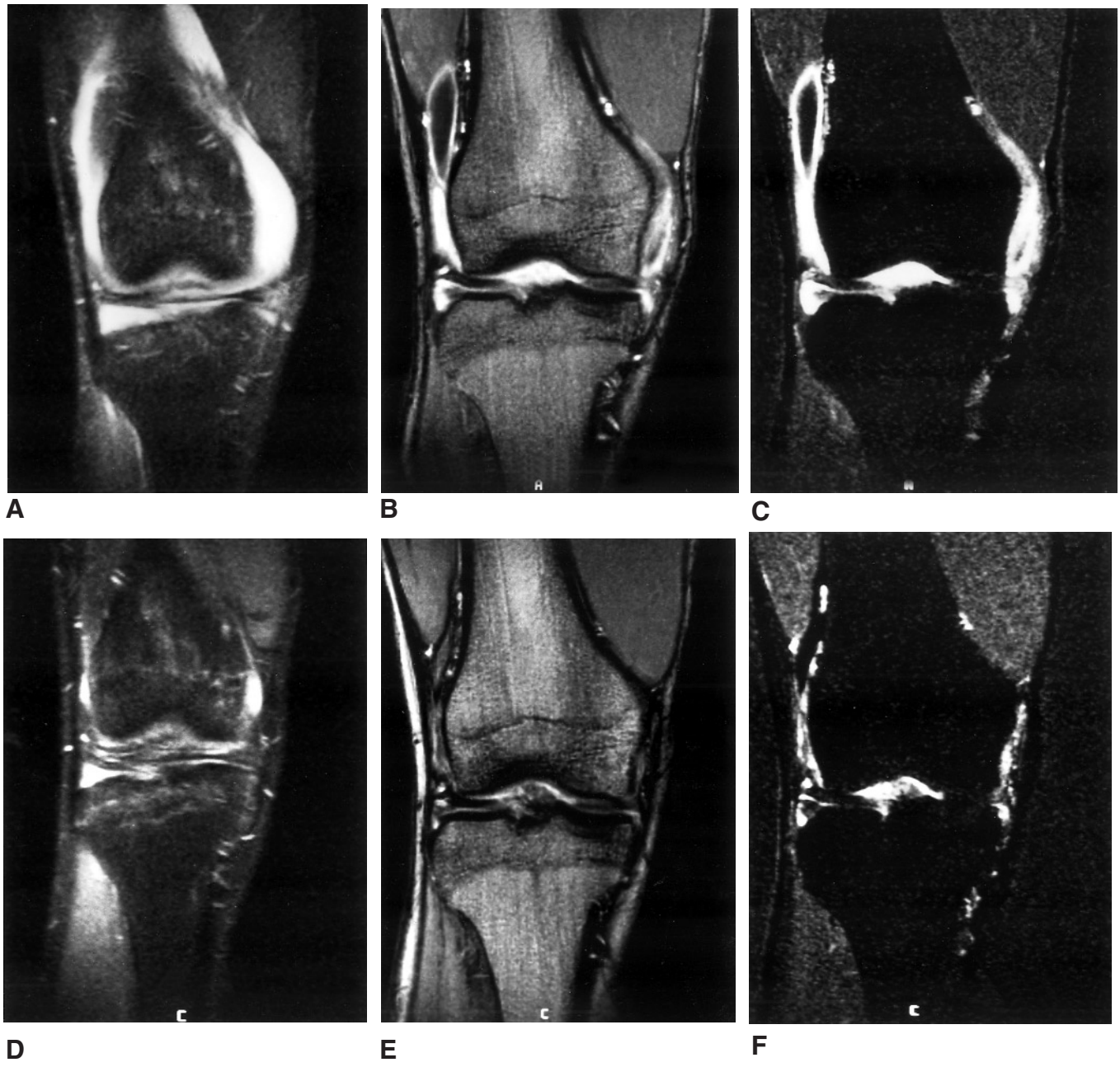
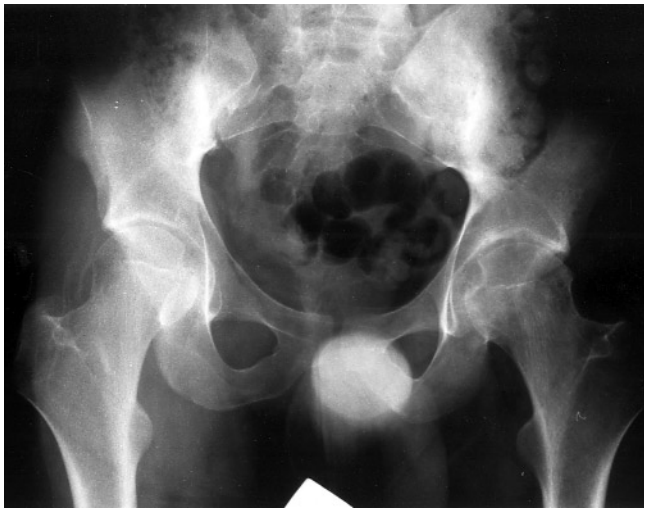


Figure 4. MRI of a 21-year-old HLA-B27 positive male (Patient 4) with a 6 month history of right knee pain presenting after a urethral discharge and conjunctivitis. Treatment had included a course of oral antibiotics at presentation, NSAID, sulfasalazine, and 2 intraarticular cortisone injections with limited, short-lived efficacy. All images right knee. A. Coronal STIR (TR 2727, TI 150, TE 12 ms) — pretreatment baseline. Large joint effusion. B. Coronal T1 dMRI (dynamic MRI, with gadolinium augmentation) — pretreatment baseline. T1 gradient echo sequence (TR 50, TE 12 ms, flip angle 70°), performed with intravenous augmentation with gadolinium and dynamic image acquisition. C. Coronal T1 sdMRI (subtracted dynamic MRI, with gadolinium augmentation) — pretreatment baseline. This is the same image as B after subtraction. On these 2 images, bright signal represents intense augmentation of synovium. D. Coronal STIR — Day 84. Effusion has resolved. E. Coronal T1 dMRI — Day 84. F. Coronal T1 sdMRI — Day 84. This is the same image as E after subtraction. Appearances have returned to normal.

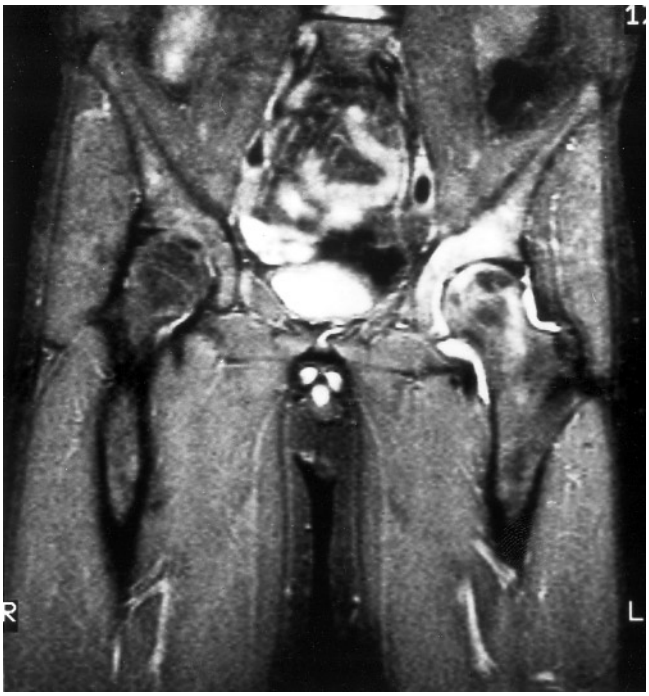
account for the more impressive effects of therapy on MR variables of inflammation in bone compared to synovium. In addition, clinical benefit was often delayed until patients had received at least 4 infusions. Consequently, more persistent therapy may be required to suppress synovitis in some patients.

Reports describing MR imaging of patients with SpA have primarily focused on the sacroiliac and knee joints

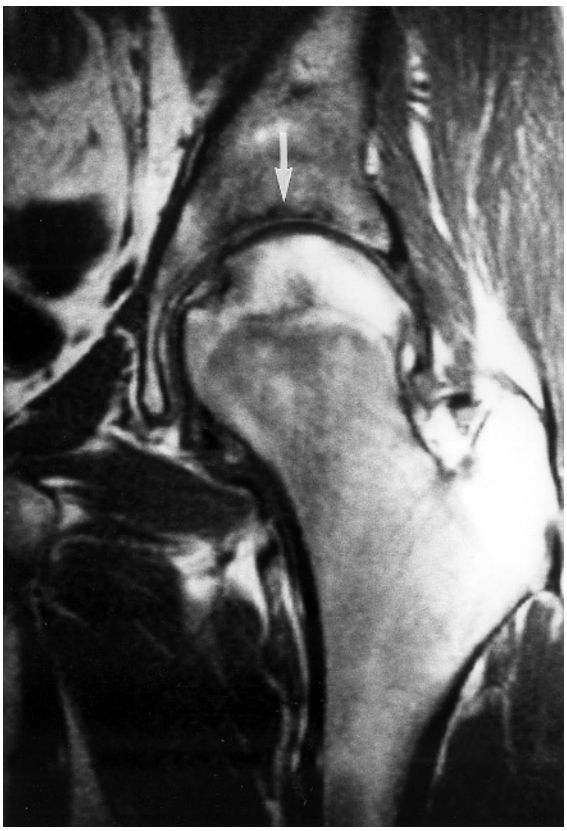
Figure 5.



A

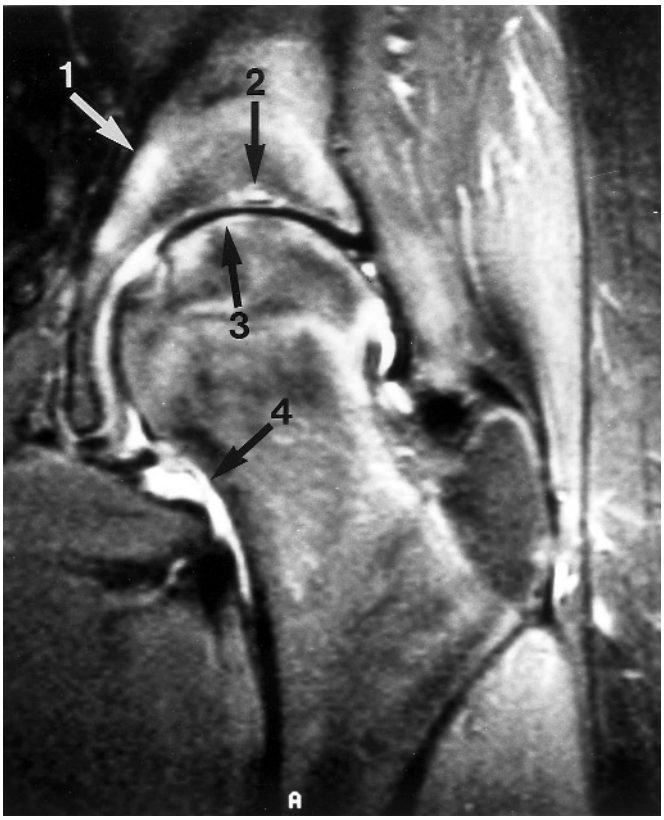


B

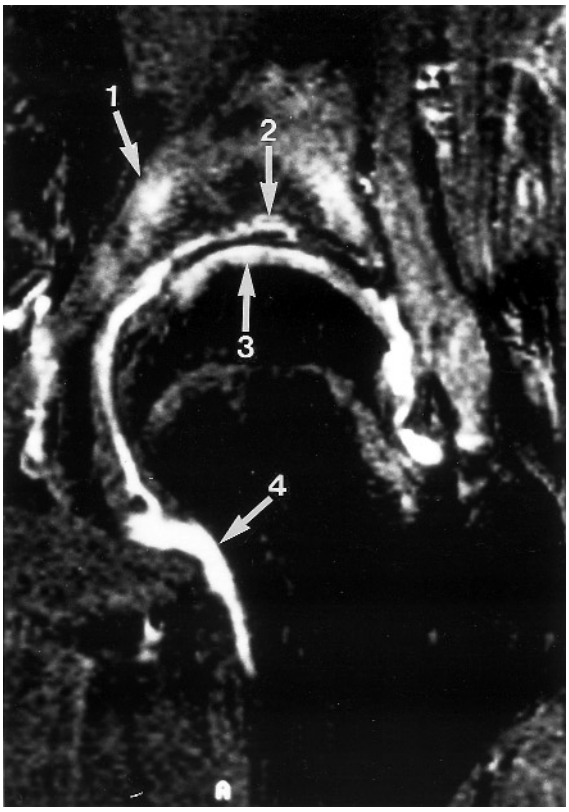


C

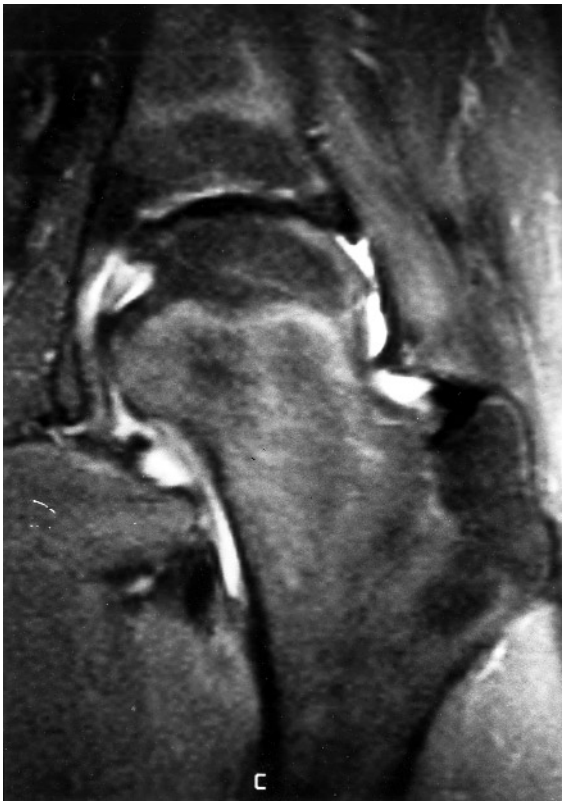
Figure 5. Images of L hip from a 19-year-old HLA-B27 positive male (Patient 8) with a 3 year history of L groin pain. Grade 2 sacroiliitis was evident on pelvic radiography but back symptoms were minimal. Initial treatment had included NSAID, intraarticular steroids under fluoroscopic guidance (× 3), and sulfasalazine, with no significant benefit and gastrointestinal intolerance to most NSAID. A. Radiograph of pelvis one year prior to entry to trial. Diffuse periarticular osteoporosis is associated with mild joint space narrowing in the left hip. Extensive erosive arthropathy is present in the SI joints. B. Coronal STIR pelvis one year prior to entry to trial. Intense bone marrow edema in the left hip involves acetabulum and femur. Joint effusion is present. Right hip is normal. C. Coronal T1 spin echo (TR 500, TE 20 ms) — pretreatment baseline. Arthropathy has resulted in near complete loss of marrow fat in the acetabulum with subchondral erosion (arrow). Patchy loss of fat signal is noted in the proximal femur. D. Coronal STIR left hip — pretreatment baseline. Findings in the left hip are similar to B. [arrows: 1. Bone marrow edema — acetabulum; 2. Bone marrow edema and subchondral erosion — acetabulum; 3. Bone marrow edema in subchondral bone of femoral head; 4. Synovial hypertrophy, inflammation, and edema. E. Coronal T1 sdMRI — pretreatment baseline. Hyperemia and inflammation are most prominent in the acetabulum (arrows 1 and 2), femoral subchondral bone (arrow 3), and synovium (arrow 4)]. F. Coronal STIR left hip — Day 84. Bone marrow edema has markedly improved. G. Coronal T1 sdMRI — Day 84. Hyperemia and inflammation in the acetabulum and femur have dramatically improved. Synovial augmentation is more intense.



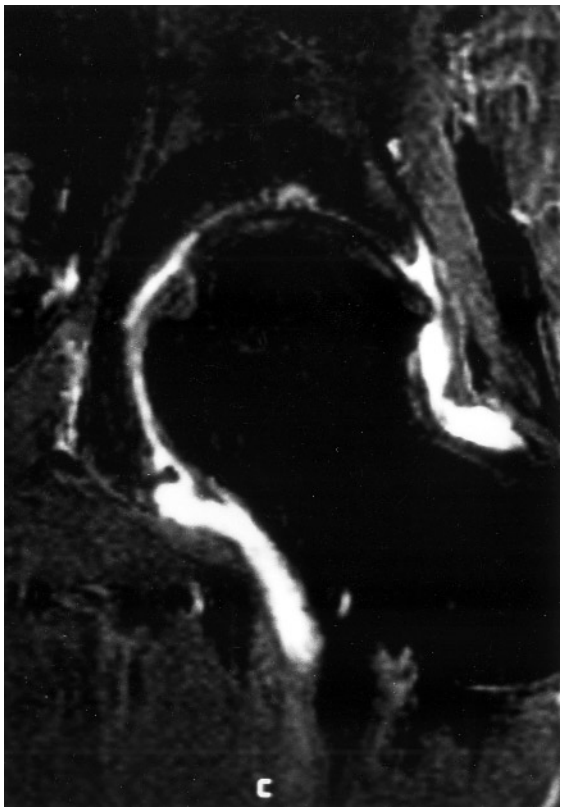
D



E



F



G

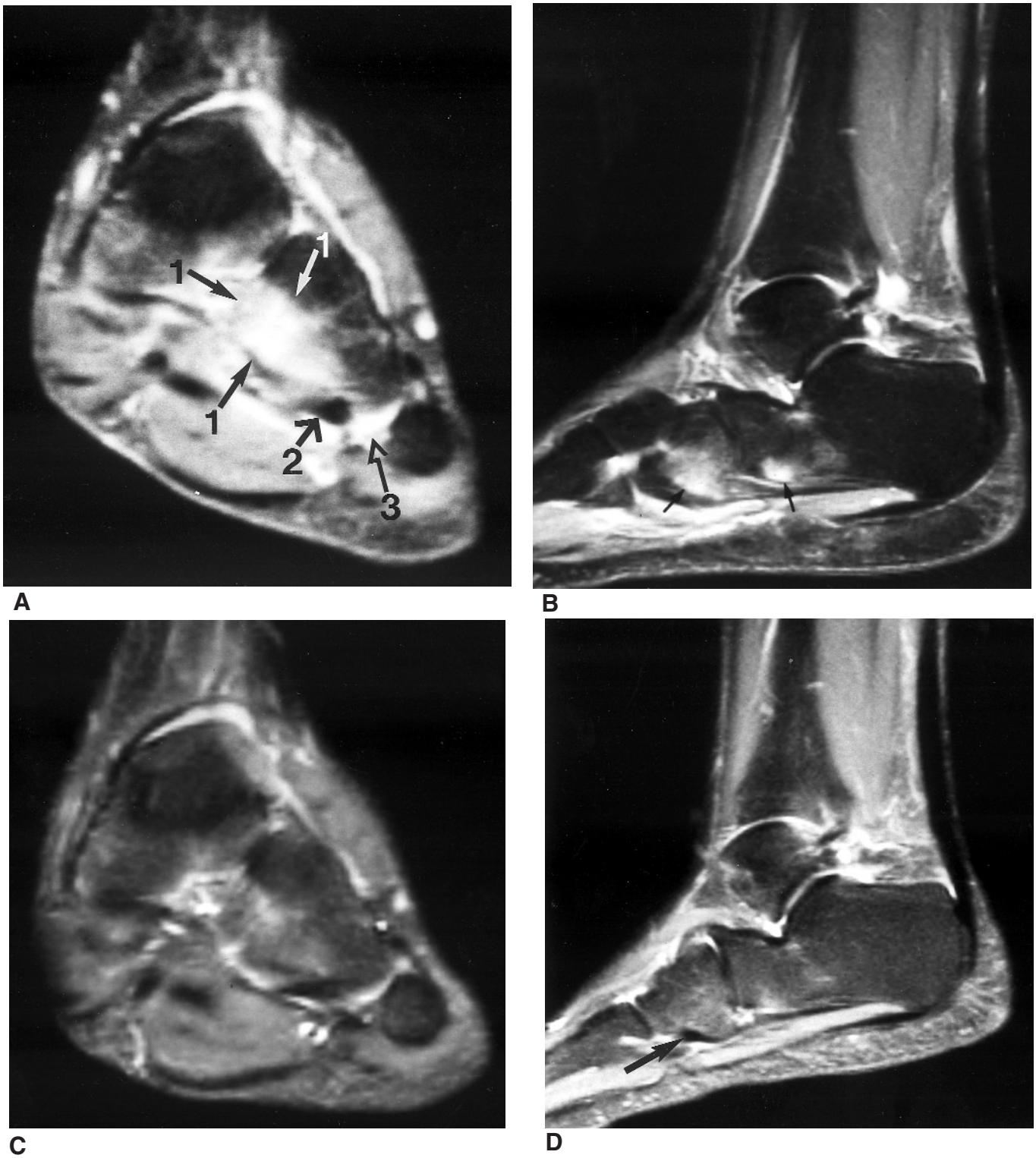


Figure 6. MRI of a 37-year-old HLA-B27 positive female (Patient 3) with a 20 year history of SpA and grade 2 changes of sacroiliitis on pelvic radiography. Peripheral joint manifestations included refractory right-sided midtarsal foot pain present for 6 years. Baseline therapy included methotrexate, sulfasalazine, and diclofenac/misoprostol. All images of the right foot and ankle. A. Coronal STIR — pretreatment baseline. Intense bone marrow edema affects the plantar half of the cuboid bone (arrows: 1. Bone marrow edema in plantar aspect of cuboid bone; 2. Peroneus longus tendon; 3. Soft tissue inflammation/edema). B. Sagittal STIR — pretreatment baseline. Edema is present in the plantar aspect of the calcaneus and cuboid bones (arrows) and adjacent soft tissues. C. Coronal STIR — Day 84. Bone marrow edema in the cuboid and soft tissue inflammation have improved. D. Sagittal STIR — Day 84. Bone marrow edema in the cuboid and soft tissue inflammation have improved (arrow: peroneus longus tendon).

using fat suppression techniques that allow the detection of bone marrow edema (STIR and T2 spin echo with spectral presaturation)[8,22]. The perientheseal bone marrow edema observed in the knee joints of patients clinically diagnosed with SpA in an early arthritis clinic[8] was readily apparent in 2 of our 3 patients with early SpA (disease duration less than 1 year). In addition, the intense subchondral femoral head augmentation with gadolinium is consistent with an earlier histopathologic report describing subchondral granulation tissue in the femoral head of a patient with early SpA undergoing cup arthroplasty[28]. MR imaging of the joints of the midfoot in SpA has, to our knowledge, not been described previously, and examination of one patient presents a peculiar picture of bone marrow edema within the cuboid and adjacent soft tissues. The tendon of the peroneus longus traverses the plantar aspect of the cuboid and is lined by fibrocartilage where it abuts against bone[29]. The cuboid periosteum lining the groove surrounding the tendon also has a layer of fibrocartilage, which is typical of wraparound tendons where they abut against bone[29]. This is consistent with reports describing extensive osteitis in the calcaneum adjacent to the periosteal fibrocartilage lining the upper two-thirds of the posterior aspect of the calcaneum[30,31].

Although previous work has shown that aminobisphosphonates, such as pamidronate, may acutely induce the generation of proinflammatory cytokines from certain cell lines[32], the effects of chronic dosing on generation of proinflammatory cytokines has not been well studied. A recent report has shown that alendronate, another bisphosphonate, given orally in high doses (40 mg/day) for 4 months, ameliorates rheumatoid arthritis (RA) and decreases ESR and CRP levels[33]. This is consistent with our data. Our data further suggest that this regime of pamidronate therapy should also be evaluated in RA for its ability to induce sustained amelioration of synovitis. In particular, recent work also highlights the common occurrence of bone edema adjacent to sites of synovitis in patients with (RA)[34].

The induction of an acute phase reaction following the first iv dose of pamidronate, with lymphopenia and elevated acute phase proteins, e.g., CRP, has been well documented[26,27]. This occurred in most of our patients. The mechanism involved presently remains unclear although aminobisphosphonates have been shown to inhibit enzymes of the mevalonate pathway that generates protein factors regulating diverse cell processes such as cell morphology, cytoskeletal arrangement, trafficking of vesicles, and apoptosis. Limited reports have stated that induction of lymphopenia is confined to the first infusion of pamidronate[26,27]. In contrast, our experience indicates that this is observed with successive infusions (data not shown). It will therefore be of interest to examine which T cell subsets are affected and whether therapy induces prolonged changes in circulating T cell subsets.

Our data provide further preliminary evidence to support a role for pamidronate in the treatment of SpA and reinforce the rationale for double blinded evaluation. The likelihood of acute arthralgias, myalgias, and pyrexia following the first infusion of pamidronate, however, precludes the use of placebo controls, as it is difficult to ensure effective patient blinding. A dose response format may, therefore, be more appropriate.

REFERENCES

1. Bjarnason I, Zanelli G, Prouse P, et al. Blood and protein loss via small intestine inflammation induced by nonsteroidal anti-inflammatory drugs. Lancet 1987;2:711-4.
2. Bjarnason I, Hayllar J, Macpherson A, Russell AS. Side effects of NSAIDs on the small and large intestine in humans. Gastroenterology 1993;104:1832-947.
3. Amor B, Dougados M, Khan MA. Management of refractory ankylosing spondylitis and related spondyloarthropathies. Rheum Dis Clin North Am 1995;21:117-28.
4. Dougados M, van der Linden S, Leirisalo-Repo M, et al. Sulphasalazine in the treatment of spondyloarthropathy. Arthritis Rheum 1995;38:618-27.
5. Clegg DO, Reda DJ, Weisman MH, et al. Comparison of sulphasalazine and placebo in the treatment of ankylosing spondylitis. Arthritis Rheum 1996;39:2004-12.
6. Dougados M, Maetzel A, Mijiyawa M, Amor B. Evaluation of sulphasalazine in the treatment of spondyloarthropathies. Ann Rheum Dis 1992;51:955-8.
7. Neure L, Francois RJ, Bywaters R, Sieper J, Braun J. Further characteristics of sacroiliac inflammation in ankylosing spondylitis [abstract]. Clin Rheumatol 1998;17:443.
8. McGonagle D, Gibbon W, O'Connor P, Green M, Pease C, Emery P. Characteristic magnetic resonance imaging entheseal changes of knee synovitis in spondyloarthropathy. Arthritis Rheum 1998;41:694-700.
9. Schichikawa K, Tsyimoto M, Nishioka J, Nishibayashi Y, Matsumoto K. Histopathology of early sacroilitis and enthesitis in akylosing spondylitis. In: Ziff M, Cohen SB, editors. Advances in inflammation research. Vol 9. The spondyloarthropathies. New York: Raven Press; 1985:15-24.
10. Sansoni P, Passeri G, Fagnoni F, et al. Inhibition of antigen-presenting cell function by alendronate in vitro. J Bone Min Res 1995;10:1719-25.
11. Pennanen N, Lapinjoki S, Urtti A, Monkkonen J. Effect of liposomal and free bisphosphonates on the IL-1ß, IL-6, and TNF-α secretion from RAW 264 cells in vitro. Pharm Res 1995;12:916-22.
12. Kinne RW, Schmidt CB, Buchner E, Hoppe R, Nurnberg E, Emmrich F. Treatment of rat arthritides with clodronate-containing liposomes. Scand J Rheumatol 1995;24 Suppl:91-7.
13. Glatt M, Blatter A, Bisping M, Bray MA. Effects of diphosphonates (APD, EHDP) on inflammation and bone turnover in adjuvant arthritis rats [abstract]. Experientia 1983;39:681.
14. Eggelmeijer F, Papapoulos SE, van Paassen HC, Dijkmans BAC, Breedveld FC. Clinical and biochemical response to single infusion of pamidronate in patients with active rheumatoid arthritis: a double blind placebo controlled study. J Rheumatol 1994; 21:2016-20.
15. Maccagno A, DiGiorgio E, Roldan EJA, Caballero LE, Lloret AP. Double blind radiological assessment of continuous oral pamidronic acid in patients with rheumatoid arthritis. Scand J Rheumatol 1994;23:211-4.
16. Ralston SH, Hackling L, Willocks L, Bruce F, Pitkeathly DA. Clinical, biochemical, and radiographic effects of aminohydroxypropylidene biphosphonate treatment in rheumatoid arthritis. Ann Rheum Dis 1989;48:396-9.

17. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gasford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: The Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
18. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: The development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
19. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Global Score (BAS-G). Br J Rheumatol 1996;35:66-71.
20. Braun J, Bollow M, Eggens U, Konig H, Distler A, Sieper J. Use of dynamic magnetic resonance imaging with fast imaging in the detection of early and advanced sacroiliitis in spondyloarthropathy patients. Arthritis Rheum 1994;37:1039-45.
21. Bollow M, Braun J, Taupitz M, et al. CT-guided intraarticular corticosteroid injection into the sacroiliac joints in patients with spondyloarthropathy: indication and follow-up with contrast-enhanced MRI. J Comput Assist Tomogr 1996;20:512-21.
22. Blum U, Buitrago-Tellez C, Mundinger A, et al. Magnetic resonance imaging (MRI) for detection of active sacroiliitis — a prospective study comparing conventional radiography, scintigraphy, and contrast enhanced MRI. J Rheumatol 1996:23:2107-15.
23. Bollow M, Braun J, Hamm B, et al. Early sacroiliitis in patients with spondyloarthropathy: Evaluation with dynamic gadolinium-enhanced MR imaging. Radiology 1995;194:529-36.
24. Braun J, Bollow M, Seyrekbasan F, et al. Computed tomography guided corticosteroid injection of the sacroiliac joint in patients with spondyloarthropathy with sacroiliitis: clinical outcome and followup by dynamic magnetic resonance imaging. J Rheumatol 1996;23:659-4.
25. Maksymowych WP, Jhangri GS, Le Clercq S, Skeith K, Yan A, Russell AS. An open study of pamidronate in the treatment of refractory AS. J Rheumatol 1998;25:714-7.
26. Adami S, Bhalla AK, Dorizzi R, et al. The acute phase response after bisphosphonate administration. Calcif Tissue Int 1987; 41:326-31.
27. Schweitzer DH, Oostendrop-Van de Ruit M, van der Pluijm G, Lowick CWGM, Papapoulos SE. Interleukin-6 and the acute phase response during treatment of patients with Paget's disease with the nitrogen-containing bisphosphonate dimethylaminohydroxy-propylidene bisphosphonate. J Bone Miner Res 1995;10:956-62.
28. Pasion EG, Goodfellow JW. Pre-ankylosing spondylitis. Histopathological report. Ann Rheum Dis 1975;34:92-7.
29. Benjamin M, Ralphs JR. Fibrocartilage in tendons and ligaments — an adaptation to compressive load. J Anat 1998;193:481-94.
30. Olivieri I, Barozzi L, Padula A, et al. Retrocalcaneal bursitis in spondyloarthropathy: assessment by ultrasonography and magnetic resonance imaging. J Rheumatol 1998;25:1352-7.
31. McGonagle D, Emery P. Achilles tendonitis in spondyloarthropathy [letter]. Olivieri I, Barozzi L, Pavlica P, Padula A, Salvarani C, Cantini F [reply]. J Rheumatol 1999;26:754-5.
32. Richards PJ, Amos N, Williams AS, Williams BD. Pro-inflammatory effects of the aminobisphosphonate ibandronate in vitro and in vivo. Rheumatology 1999;38:984-91.
33. Cantatore FP, Acquista CA, Pipitone V. Evaluation of bone turnover and osteoclastic cytokines in early rheumatoid arthritis treated with alendronate. J Rheumatol 1999;26:2318-23.
34. McGonagle D, Conaghan PG, O'Connor P, et al. The relationship between synovitis and bone changes in early untreated rheumatoid arthritis. A controlled magnetic resonance imaging study. Arthritis Rheum 1999;42:1706-11.