

Assessment of the efficacy of pamidronate in ankylosing spondylitis: an open prospective trial

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ABSTRACT

Introduction: Bisphosphonates have anti-inflammatory properties in arthritic conditions. This study was conducted to assess the therapeutic potential of intravenous pamidronate in nonsteroidal anti-inflammatory drug (NSAID) refractory or intolerant cases of ankylosing spondylitis (AS).

Methods: A total of 35 NSAID refractory/intolerant AS patients with Bath AS Disease Activity Index (BASDAI) score 4 or above were recruited for the study. Monthly pamidronate infusions (60 mg) were administered to the patients for six months. Treatment outcomes were assessed by comparing baseline values with the values after six infusions using BASDAI, Bath AS Functional Index (BASFI), Metrology Index (BASMI) and Global Score (BAS-G), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). An improvement was defined according to the Assessments in Ankylosing Spondylitis (ASAS)-20 and BASDAI-50.

Results: 26 patients received all the six infusions. Of these, 22 (85 percent) achieved ASAS-20 and 20 (77 percent) achieved BASDAI-50 responses. Decrements were noted in the mean BASDAI (56.4 percent), BASFI (52.66 percent), BASMI (55.72 percent), BAS-G (66.71 percent), ESR (52.12 percent) and CRP (72.84 percent) after six months. The tender and swollen joint counts of 14 (54 percent) patients with peripheral arthritis were respectively reduced to a mean value of 0.85 and nil, from the baseline of 2.57 and 1.2. Early feel good response was noted in 16 (62 percent) patients within 48 hours of the first infusion. Fever, arthralgia and myalgia were observed in six cases after the first infusion, and in one case, after the second infusion. These symptoms resolved spontaneously within 24 hours.

Conclusion: Intravenous pamidronate has good efficacy for the treatment of AS.

Keywords: ankylosing spondylitis, pamidronate, tumour necrosis factor-alpha

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INTRODUCTION

Ankylosing spondylitis (AS) is the prototype of spondyloarthritides. It affects the axial skeleton, peripheral joints and extraarticular structures. Although the pathogenesis of AS is immune mediated, it is incompletely understood. Tumour necrosis factor (TNF)- α is thought to play a role in its pathogenesis. The treatment of AS is based on peripheral joint or axial involvement. For peripheral joint involvement, nonsteroidal anti-inflammatory drugs (NSAIDs) and sulfasalazine are recommended, whereas for spinal AS, anti-TNF- α should be considered if the patient is resistant to NSAIDs. Failure of NSAIDs is fairly common. Gastrointestinal side effects also limit their long-term use. TNF- α antagonists are highly effective in AS but are much more expensive than NSAIDs. They are contraindicated in patients with tuberculosis, multiple sclerosis, lupus and malignancy.

Recently, the bisphosphonate group of agents have emerged owing to their anti-inflammatory properties in arthritic conditions, in addition to their anti-osteoclastic effects. The anti-inflammatory properties of bisphosphonate are due to its inhibition of macrophage migration to the site of inflammation, inhibition of generation of proinflammatory cytokines such as interleukin (IL)-1, TNF- α and IL-6, as well as its dose-dependent inhibition of the antigen-presenting function of peripheral blood monocytes.⁽¹⁻³⁾ Pamidronate, a bisphosphonate, can also stimulate polymorphonuclear leucocyte and platelet-derived nitric oxide production, which could act as a negative feedback signal to restrict the inflammatory process and constitute a protective mechanism against bone resorption occurring during inflammation.⁽⁴⁾ With the anti-inflammatory property of bisphosphonate in mind, we conducted this study to

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Table I. Mean values of disease activity and functional indices during follow-up of the 26 patients who received all six infusions.

Parameter	Mean value \pm 2SD (SD)		Percentage of reduction in mean scores	p-value
	Baseline	After six months of pamidronate therapy		
BASDAI	6.76 \pm 2.8 (1.40)	2.95 \pm 1.05 (0.52)	56.36	< 0.001
BASFI	6.38 \pm 3.13 (1.56)	3.02 \pm 1.16 (0.58)	52.66	< 0.001
BASMI	4.72 \pm 3.46 (1.73)	2.09 \pm 2.6 (1.30)	55.72	< 0.001
BAS-G	7.09 \pm 2.78 (1.39)	2.36 \pm 1.42 (0.71)	66.71	< 0.001
ESR (mm/hr)	51.27 \pm 26.35 (13.176)	24.55 \pm 17.07 (8.536)	52.12	< 0.001
CRP (mg/L)	30.45 \pm 18.79 (9.39)	8.27 \pm 3.11 (1.55)	72.84	< 0.001

SD: standard deviation; BASDAI: Bath ankylosing spondylitis disease activity index; BASFI: Bath ankylosing spondylitis functional index; BASMI: Bath ankylosing spondylitis metrology index; BAS-G: Bath ankylosing spondylitis global index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

assess the efficacy of intravenous (IV) pamidronate in NSAID-resistant or NSAID-intolerant AS patients.

METHODS

A total of 35 patients, who fulfilled the modified New York criteria for AS but failed to respond to NSAIDs or were intolerant to NSAIDs, were recruited for the study.⁽⁵⁾ Patients aged 16–60 years from both genders were selected for the study. They must also have active disease, defined as Bath AS disease activity index (BASDAI) \geq 4 measured twice, one month apart. Patients were also either nonresponsive or incompletely responsive (incomplete relief of pain, stiffness or constitutional symptoms) to adequate doses of more than two NSAIDs (used sequentially) for at least three months.

Initially, either indomethacin, diclofenac or etodolac was used to treat 71 AS patients. The dosage of each drug was gradually increased to relieve the symptoms until the maximum tolerable dose (indomethacin 200 mg/day, diclofenac 200 mg/day or etodolac 1,200 mg/day). If inadequate response was observed, other NSAIDs were used. In five patients, NSAIDs were stopped due to abdominal pain and upper gastrointestinal bleeding, and they were subsequently recruited for pamidronate therapy. 32 patients were nonresponsive or incompletely responsive to NSAIDs. Patients who responded favourably ($n = 34$) to NSAIDs were excluded from the study, and their dosage of NSAIDs were reduced gradually. Two patients who did not respond to NSAIDs received TNF- α blocker (infliximab). Pamidronate therapy was provided in patients who could not afford TNF- α blockers. NSAIDs were stopped during treatment with pamidronate.

The exclusion criteria were patients with renal impairment, end-stage AS, skeletal deformity other than AS, stage 3 or 4 congestive heart failures (for fear of fluid overload during pamidronate infusion), and

women of childbearing age or planning to conceive.

The treatment regimen comprised monthly infusions of pamidronate 60 mg (Pamidro, Medicon Pharma Lab, Chennai, Tamil Nadu, India) in 500 ml of normal saline over four hours for a period of six months. The medication was administered after obtaining informed consent from the patients. Sulfasalazine and methotrexate were continued in 14 AS cases (40%) for peripheral arthritis. An initial assessment was conducted before pamidronate was administered, and then at monthly intervals. The total observation period was six months. The final assessment was conducted one month after the sixth dose of pamidronate.

The assessments were conducted using Bath AS Disease Activity Index (BASDAI) for the measurement of disease activity, Bath AS Functional Index (BASFI) for the measurement of functional impairment, Bath AS Metrology Index (BASMI) for the measurement of spinal mobility and Bath AS Global Score (BAS-G) for global assessment of wellbeing.⁽⁶⁻⁹⁾ BAS-G was assessed by a separate investigator. For all the parameters, the scoring range was 0–10, where a higher score indicated greater severity of the disease. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured every month. The response was measured by comparing the baseline values with the values obtained after completing six cycles of treatment. Improvement was defined according to the Assessments in Ankylosing Spondylitis (ASAS) Working Group criteria (ASAS-20).⁽¹⁰⁾ A 50% improvement in BASDAI was considered as another parameter of improvement (BASDAI-50).

GraphPad QuickCalcs software (Graphpad Software Inc, La Jolla, CA, USA) was used for statistical analysis. For the description of data, mean values, percentages and standard deviations were used. Data was expressed as mean \pm 2SD (including 95% of values). Student's *t* test was used for the assessment of statistical significance.

Table II. Comparison of improvements in AS patients with pamidronate therapy in various studies.

Study	Duration	BASDAI	BASFI	BASMI	BAS-G	ASAS-20	BASDAI-50	ESR	CRP	Peripheral joint symptoms
Maksymowych et al ⁽¹⁶⁾	Observation at 6 mths	SI (p = 0.03) vs. NS (p = 0.07); improvement in group I is 30%.	-	SI (p = 0.01) vs. SI (p = 0.007)	-	-	-	SI (p = 0.009) vs. NS (p = 0.12)	-	-
Maksymowych et al ⁽¹⁷⁾	Observation at 84 days	SI (44.2%)	SI (47.3%)	-	SI (42.2%)	-	-	SI (49.4%)	SI (66.9%)	SI (SJC 93.8%; TJC 98.2%)
Maksymowych et al ⁽¹⁸⁾	6 mths	SI (34.5% in the 60 mg group and 15% in the 10 mg group, p = 0.002)	Greater reductions in 60 mg group (30.3% vs. 2.8%, p < 0.001)	Greater reductions in 60 mg group (p = 0.03)	Greater reductions in 60 mg group (p = 0.002)	-	16/41 (39%) vs. 7/43 (16.3%, p = 0.027)	NS	NS	NS
Haibel et al ⁽¹⁹⁾	Observation up to 6 mths	SI (16.36% at 3 mths, 14.55% at 6 mths)	NS	NS	SI (26.08% at 1 mth, 21.74% at 2 mths)	4/9 at 6 mths	3/9 at 6 mths	NS	NS	NS
Cairns et al ⁽²⁰⁾	6 mths	SI (15.44%)	-	NS	-	-	-	NS	NS	-
Malaviya et al ⁽²¹⁾	6 mths	-	-	-	-	39/46 (85%)	39/46 (85%)	-	-	-
Present study	6 mths	SI (56.3%)	SI (52.66%)	SI (55.72%)	SI (66.71%)	22/26 (85%)	20/26 (77%)	SI (52.12%)	SI (72.84%)	SI (SJC 66.93%; TJC 100%)

Note: Percentage of mean decrement of parameters is mentioned (where exact values are available). For ASAS-20 and BASDAI 50, the ratio of improved patients is mentioned (cases with the response/cases under observation).

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BAS-G: Bath Ankylosing Spondylitis Global Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SI: significant improvement; NS: not significant (data not available); SJC: swollen joint count; TJC: tender joint count

RESULTS

In all, 35 AS patients were enrolled in the study. The mean age of the patients (male:female ratio 32:3) was 32.6 ± 15.76 years and the mean disease duration was 6.4 ± 3.6 years. The mean baseline disease activity and functional indices were as follows: BASDAI 6.76; BASFI 6.38; BASMI 4.72; BAS-G 7.09; ESR 51.27 mm/hr; and CRP 30.45 mg/L. Out of the 35 patients, 26 received all six of the infusions. Four patients were lost to follow-up after the first infusion. Five patients dropped out after three infusions; three patients due to a lack of efficacy and two patients due to disease flare-up.

At six months, the mean BASDAI decreased by 3.81 (56.4%). 20 (77%) patients achieved a reduction of 50% or more in the BASDAI after six months. Significant reductions were also noted for BASFI, BASMI, BAS-G, ESR and CRP (Table I). Out of the total 26 patients who completed the full course of the pamidronate therapy, 22 (85%) patients achieved ASAS-20 and 20 (77%) patients

achieved a BASDAI-50 response. Early symptomatic benefit or a feel good response with reduction of pain and stiffness of spine was noted within 48 hours in 16 (62%) patients after the first dose of pamidronate infusion. After three months of follow-up, all the patients maintained their ASAS-20 and BASDAI-50 response. Of the 26 patients, 14 had peripheral joint involvement. The mean baseline tender and swollen joint counts of these 14 patients were reduced from 2.57 and 1.2 to 0.85 and nil, respectively, after six infusions. The mean tender and swollen joint counts decreased by 66.9% ($p < 0.001$) and 100% ($p < 0.001$), respectively.

Adverse events reported after IV pamidronate were minimal. Among the 26 patients, mild fever, arthralgia and myalgia were noted in six (23%) patients after the first infusion and in one (4%), after the second infusion. These symptoms resolved spontaneously within 24 hours with paracetamol. Adverse events were not prominent due to the baseline disease symptoms. Transient elevation

of liver enzymes (aspartate amino transferase and alaine amino transferase) two-folds above the normal level was noted in two patients after the second or third infusions.

DISCUSSION

Bisphosphonates have been shown to reduce chronic inflammation in animal models with established arthritis.⁽¹¹⁻¹⁵⁾ Subsequent clinical trials of pamidronate in AS patients are showing promising results. Improvements in different parameters in AS patients after pamidronate therapy in different studies are shown in Table II. Maksymowych et al, in three single-centre Canadian studies, reported the effectiveness of pamidronate in NSAID refractory AS patients.⁽¹⁶⁻¹⁸⁾ Delayed but long-lasting effects of pamidronate were observed after six months of IV pamidronate therapy.^(16,18) A 60 mg dose of IV pamidronate was significantly superior to a lower dose (10 mg).⁽¹⁸⁾ Improvement was seen mainly for axial symptoms,⁽¹⁸⁾ and the effects were less prominent at three months.^(16,18) An intensive regime (60 mg at one, two, 14, 28 and 56 days) was also effective, with significant improvement in the mean scores of BASDAI, BASFI, BAS-G, ESR and CRP level, as well as significant reduction in the mean tender and swollen peripheral joint counts after 84 days of follow up.⁽¹⁷⁾

Haibel et al, in an open observational study with pulse IV pamidronate in AS patients, found significant reductions in the mean BASDAI scores at the end of six months and a 20% improvement in ASAS in four out of nine patients.⁽¹⁹⁾ In a study of 15 AS patients by Cairns et al, significant improvement was noted in BASDAI score (but not in BASMI, CRP or ESR) after six months of pulse IV pamidronate (60 mg) therapy.⁽²⁰⁾ In a study by Malaviya et al, significant improvement was noted with combined pamidronate and methylprednisolone therapy in 46 AS patients. Out of the 46 patients, 39 achieved ASAS-20 and BASDAI-50 responses (85%, 95% confidence interval 71%–94%), and seven (15%) patients failed to improve.⁽²¹⁾

The most common adverse events reported after IV pamidronate are flu-like syndrome with a spike in fever, arthralgia and myalgia.⁽²⁰⁾ These are largely limited to the first infusion. Transient arthralgia or myalgia has been observed after the first infusion in 68.3% of patients.⁽¹⁸⁾ In our study, out of a total of 35 patients, 26 patients completed the full course of pamidronate therapy. The response rate was significant; 22 (85%) patients achieved ASAS-20 and 20 (77%) achieved BASDAI-50 response. Feel good response was noted in the majority of patients (62%) shortly after receiving the first dose. The tolerability was excellent. Minimal

self-limiting adverse side effects, such as post-infusion fever, arthralgia and myalgia, were seen in only six cases after the first infusion and in one case after the second infusion, and these side effects persisted for one to two days. No patient required discontinuation of therapy due to adverse events.

In conclusion, pulse pamidronate therapy leads to significant clinical improvement in patients with AS, with reduction of both axial and peripheral joint symptoms. Apart from the quantification of improvements in BASDAI, BASFI, BASMI, BAS-G, ESR and CRP, what is more important is the early symptomatic relief, such as the feel good factor for distressed patients after the first dose of pamidronate therapy. Mild post-infusion myalgia, arthralgia and fever are the common adverse effects, but discontinuation of therapy is usually not required.

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