Original article

Intravenous pamidronate for refractory rheumatoid arthritis

Mansour Salesi[1], Peyman Mottaghi[2], Mansour Karimifar[1], Ziba Farajzadegan[3]

[1]Assistant Professor, Department of Rheumatology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
[2]Associate Professor, Department of Rheumatology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.
[3]Associate Professor, Department of Community Medicine, School of Medicine, Isfahan University of Medical Sciences, Isfahan Iran.

Background: Patients with rheumatoid arthritis may be resistant to conventional treatment with disease-modifying antirheumatic drugs (DMARDs). On the other hand, biologic therapy is costly and may be inconvenient for many patients. Pamidronate is a potent bisphosphonate with the capacity of modifying the biological activity of the immune system cells. It may thus be used as an anti-inflammatory agent in patients with inflammatory joint diseases. **Materials and Methods:** To assess the effectiveness of pamidronate in the management of rheumatoid arthritis, we selected 38 patients with rheumatoid arthritis to enroll in a pilot study to receive pamidronate and conventional treatment with prednisolone and DMARDs in combination. These patients received 60 mg of pamidronate for 3 consecutive months and were followed for 6 months since the first infusion. **Results:** The mean visual analogue score (VAS) and disease activity score (DAS28) fell steadily until one month after the third infusion. However, no improvements were observed during the 3 months after the last infusion of the drug. All patients, except one, reported decreased pain in response to 3 consecutive pulses of pamidronate and most had improvements in the assessed laboratory and clinical indices. The drug was tolerated well in our patients. **Conclusion:** Pamidronate infusions had beneficial effects on various clinical and laboratory parameters of patients, but alleviation of symptoms were temporary and did not last for more than 6 months. This treatment option can be a choice for difficult cases of rheumatoid arthritis with severe pain and osteoporosis.

Key words: Rheumatoid Arthritis, Refractory, Pamidronate.

INTRODUCTION

Rheumatoid arthritis, as a chronic, systemic, inflammatory disease, affects nearly 1% of the adult population and can lead to substantial disability worldwide.[1] No drug cures rheumatoid arthritis and the maintenance or induction of remission with disease-modifying antirheumatic drugs (DMARDs) is sometimes difficult.[2] Recent research has suggested a common osteoclast cellular pathway for erosions and osteoporosis in rheumatoid arthritis, both of which are mediated by the cellular action of osteoclasts.[1,3,4]

A group of potent inhibitors of osteoclasts are bisphosphonates. Pamidronate disodium, as a second-generation intravenous preparation of bisphosphonates, has been found to be safe as well as effective in the treatment of Paget's disease of the bone and osteolytic bone lesions from breast cancer or multiple myeloma.[5,6] The efficacy of pamidronate in patients with spondyloarthropathy,[7] mechanical back pain,[8] and Charcot arthropathy[9,10] has been shown in recent reports. Nevertheless, there is also experimental evidence that pamidronate possesses other different extra-skeletal effects, ranging from the capacity of modifying the biological activity of the immune system cells to influences on cells of mesenchymal origin to prevent cancer metastasis and decrease extravascular fluid accumulation in lymphedema.[11,12]

It has been shown that bisphosphonates exert their effects not only on bone tissue cells, but also on the cells of immune system. By influencing the production of pro- and anti-inflammatory cytokines, it changes the expression of molecules involved in the immune response.[13-15] Although the available data is conflicting, there has been several reports concerning the beneficial effects of bisphosphonates in controlling the progression of chronic joint inflammatory diseases, suggesting a wider use for these therapeutic agents in clinical practice.[16,17]

After the observed beneficial effects in ankylosing spondylitis, the rationale for use of pamidronate in rheumatoid arthritis is the presence of subchondral bone marrow inflammation in both diseases and high rates of bone turnover that facilitates concentration of drug within subchondral bone to modify cellular function.[18,19] Treatment with pamidronate is further reinforced by the high prevalence of osteoporosis accompanied by increased markers of bone resorption, particularly in patients with

Address for correspondence: Peyman Mottaghi, Associate Professor, Department of Rheumatology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. Email: motaghi@med.mui.ac.ir
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elevated levels of acute phase reactants.[19]

According to the available evidence and a recent report of favorable treatment response in two refractory cases of rheumatoid arthritis,[20] we propose that pamidronate might be effective, not only for the management of osteoporosis, but also as an adjunct in treatment of rheumatoid arthritis. Thus, we evaluated anti-inflammatory and analgesic properties of the pamidronate in patients with rheumatoid arthritis refractory to DMARDs and low-dose prednisolone.

MATERIALS AND METHODS

In a pilot study, a total of 79 patients were screened for eligibility to enter the study from September 2009 to October 2010. Since 51 patients did not meet the eligibility criteria, 38 patients were eventually enrolled in the study after signing written consents. The selected patients aged between 20 and 65 years and had disease duration of less than 8 years. All participants met the American College of Rheumatology (ACR) diagnostic criteria for rheumatoid arthritis and had been followed in rheumatology clinics of Isfahan University of Medical Sciences (Isfahan, Iran). They had had symptoms of active synovitis for at least 6 months and remained active despite maximum recommended or tolerated doses of DMARDs. They therefore needed to use more than 7.5 mg of prednisolone per day. Patients could receive second-line therapy (sulfasalazine, methotrexate, and hydroxychloroquine) whose provided dosage had been stable for 3 months prior to the study and remained constant for the duration of the study.

Active disease was defined as having a disease activity score 28 (DAS28) of more than 3.2. All patients were on a stable dosage of DMARDs for 2 months prior to the study and during the 3 consecutive monthly doses of pamidronate. However, whenever necessary, prednisolone dosage was increased or nonsteroidal anti-inflammatory drugs (NSAIDs) were used to control pain.

Exclusion criteria were end-stage rheumatoid arthritis (advanced disease with deformities or secondary osteoarthritis), intraarticular corticosteroid injections or intravenous (IV) infusion with methylprednisolone within the past 3 months prior to the study and during the study, serum creatinine levels higher than 1.5 mg/dl, major surgery within the previous 3 months or planned in the ensuing 6 months, severe infections/comorbidities, or active peptic ulcer disease. Patients were recruited by rheumatologists in Alzahra Hospital from both university and community-based outpatient clinics.

In a randomized, controlled trial, patients were given 40-hour long IV infusions of 60 mg of pamidronate (Aredia®-NOVARTIS) were given monthly for 3 consecutive months. Since post-infusion arthralgias and myalgias could compromise patient blinding in a placebo-controlled trial, we did not compare pamidronate with placebo. Instead, DAS28 and acute phase reactants were compared before and every months after infusion until 3 months after the last infusion. The study protocol was approved by the research ethics board of Isfahan University of Medical Sciences.

Statistical analyses

We used $SPSS_{15}$ for data analysis. For the assessment of statistical significance, the student's t and $\chi 2$ tests were applied where appropriate. P values less than or equal to 0.05 were considered significant.

RESULTS

A total number of 32 women and 6 men with a mean age of 39.4 years (range: 20-63 years) and mean disease duration of 5.4 years (range: 2-8 years) were studied. All except two patients had positive rheumatoid factor. The baseline characteristics of patients treated with pamidronate are shown in Table 1.

Table 1. Demographic and clinical characteristics of pamidronate treated patients at base line

Patients	n = 38
Mean age, years	39.4 (18-63)
No. of men / no. of women	6/32
Mean disease duration, years	5.4 (2.1-8.5)
Mean no. tender joints	13.1± 5
Mean no. swollen joints	9.4 ± 5.7
Treatment, no	
Methotrexate	36
Sulfasalazine	30
Hydroxychloroquine	12
Cyclosporine A	6
Prednisolon	38

Most patients (36 out of 38) were receiving methotrexate at study entry, 28 patients were receiving concomitant methotrexate therapy and sulfasalazine, 12 were receiving sulfasalazine, methotrexate, and hydroxychloroquine, and 6 were receiving methotrexate plus cyclosporine in full tolerated dose. All of these patients received equal to or more than 5 mg/day prednisolone and 15 patients needed to use 10 mg or more prednisolone per day to alleviate pain and morning stiffness.

All patients, except one, reported decreased pain and most had improvement in the assessed laboratory and clinical indices. Alleviation of pain and swelling generally began after first infusion of pamidronate and continued until one month after the last infusion. Swollen joint count and number of tender joints decreased after the first infusion and this trend continued until the third infusion. However, no significant improvements were observed after the third infusion of pamidronate. Mean visual analogue score (VAS) and DAS28 were 73 and 6.4 correspondingly at study entry. The values fell steadily until one month after the third infusion. No incremental changes were detected in the three months after the last infusion of the drug. According to ACR20, disease improvement was defined as at least 20% improvement in clinical and laboratory indices.[2] The mean DAS28 decreased 38% after the third infusion of the drug and 26% of patients reached DAS < 2.6 after 3 consecutive infusions of pamidronate. This was accompanied by significant reductions in swollen (53%; $p < 0.001$) and tender joint counts (66%; $p < 0.001$).

Statistical analyses showed that changes in DAS28 and all other follow-up indices continued until after the second infusion of the drug. After the third infusion however, no changes appeared. Moreover, two months after the last infusion, some increases in clinical and laboratory indices of disease activity were observed. Changes of outcome variables during and three months after treatment with pamidronate are represented in Table 2. The mean score for joint pain (VAS) decreased by 28.1 one month after the third infusion of pamidronate ($P \leq 0.003$). The mean number of tender joints decreased by 4.6 at the end of the third infusion of pamidronate ($P \leq 0.001$). The mean erythrocyte sedimentation rate (ESR) differed significantly until the third infusion, but did not change significantly thereafter (Table 2). General trends of changes in ESR, score of pain (VAS), and number of tender joints in response to three consecutive pulses of pamidronate are showed in Figure 1.

Although flu-like syndrome is a common adverse effect for parenteral bisphosphonates, most of our patients (97%) tolerated this treatment well. Our patients reported adverse reactions including transient myalgia and arthralgia, most often after the first IV infusion. This was reported in 48% of our patients whom received pamidronate as the 60-mg dose schedule but for all of these patients it was mild and tolerable and drug was not discontinued.

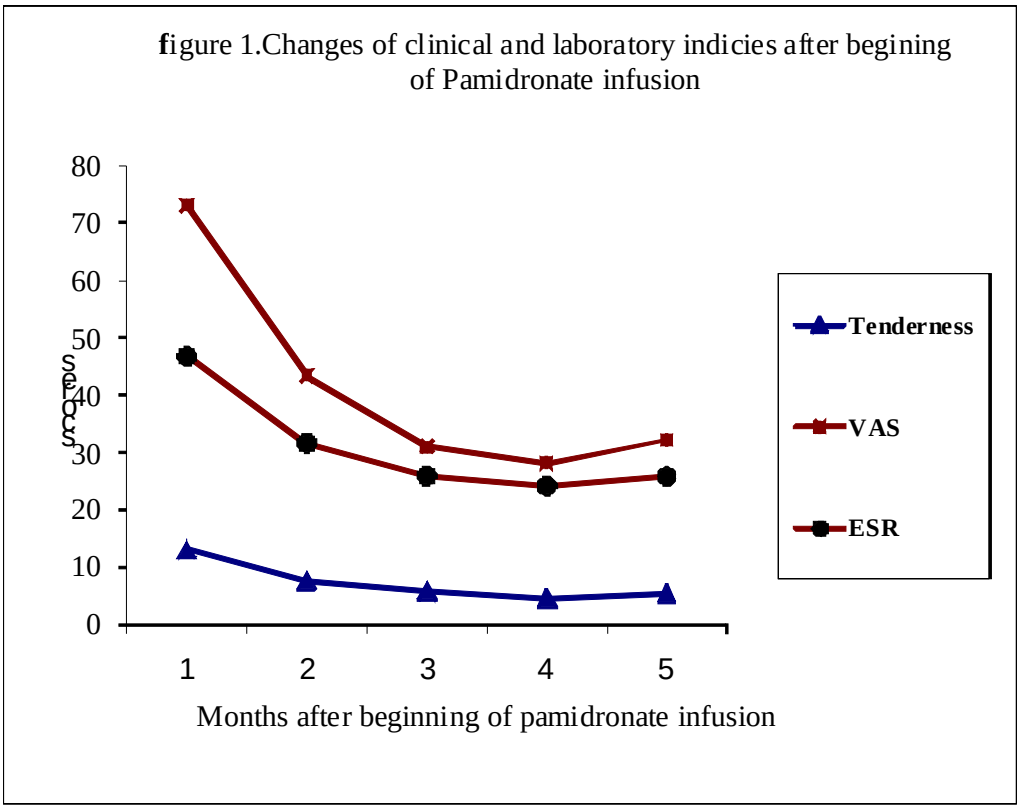

Figure 1. Changes of laboratory and clinical indices after the beginning of pamidronate infusion VAS: Visual analogue score ESR: Erythrocyte sedimentation rate

Table 2. Outcome variables during and three months after treatment with pamidronate

	Baseline	Three Mo.*		Six Mo.*	
Scores	Mean ± SD	Mean ± SD	*p*	Mean ± SD	*p*
Swollen joint	9.4 ± 5.7	4.8 ± 4.6	< 0.001	5.2 ± 5.3	< 0.001
Tender joint	13.1 ± 5	4.6 ± 4.2	0.003	5.5 ± 5	0.014
VAS [a]	79 ±15.8	28.1±21.9	0.004	32 ± 24	0.044
DAS28 [b]	6.45 ± 0.8	4 ±1.4	0.001	4.2 ±1.5	0.043
ESR	47.2 ± 20.4	24.2 ±13.9	< 0.001	25.8 ±14.1	0.029

***** Months After first infusion
[a] Visual Analogue Score
[b] Disease Activity Score

DISCUSION

Bone erosions and osteopenia are common consequences of rheumatoid arthritis[1,3] which have been suggested to be mediated by action of osteoclasts.[1,4] Due to the role of osteoclast in development of erosions and osteoporosis,[21] the possible therapeutic effects of osteoclast inhibition by pamidronate on disease activity in rheumatoid arthritis patients have been evaluated.

In early experiments in vitro, pamidronate was shown to be a potent substance in suppressing costimulatory activity of T cells, migration and proliferation of inflammatory cells, and inhibiting the secretion of proinflammatory cytokines.[14,22-23] This could reflect the possible mechanism through which pamidronate exerts its symptom-modifying effects, when it accumulates at sites of high bone turnover in subchondral bone, as well as its probable indirect effects on the adjacent synovitis in rheumatoid arthritis.[24]

The limited benefits or apparent lack of efficacy demonstrated in some clinical trials of pamidronate in rheumatoid arthritis,[25] together with the data provided by Valleala and et al.,[17] cast doubts on the benefits of bisphosphonate therapy for erosive arthritis. However, choice of bisphosphonates and dosage for their optimal use warrant further reexamination.

A previous study has shown that pamidronate significantly reduced bone marrow edema in the affected joints in ankylosing spondylitis.[7] This therapy induced less impressive anti-inflammatory effects within the adjacent synovium, but it was accompanied by significant reduction in acute phase reactants including C-reactive protein (CRP).[18,26] In particular, induction of apoptosis and suppression of proinflammatory cytokines appear to be the dose-dependent properties of bisphosphonates.[16] However, high serum levels obtained by IV administration may be relevant to the therapeutic effects observed with pamidronate. Whether this could be associated with an anti-inflammatory effect in rheumatoid arthritis is presently speculative, although it would be consistent with the more impressive anti-inflammatory effects observed with a more intensive regimen of pamidronate administration.

A recent report has described dose-dependent, anti-inflammatory effects of bisphosphonates in chronic inflammatory arthritis by suppression of acute-phase reactants, as well as beneficial clinical responses with high-dose alendronate therapy (40 mg/day) after 30 days, compared to placebo, in 32 patients with rheumatoid arthritis.[19] Another clinical trial of bisphosphonates in rheumatoid arthritis with etidronate showed a decline in mean prednisone dose over the two-year duration of the trial. However, it could not detect significant differences in CRP, joint erosion, or DAS28 in patients compared to the control group.[17]

As our data showed, this treatment significantly reduced pain in patients with resistant rheumatoid arthritis and caused an improvement of DAS28 in most participants. Reductions in ESR were also significant among these patients. A time and cumulative dose-dependent fall in the mean DAS28 was observed during the 3 months of pamidronate administration. Changes of all clinical indices (swollen and tender joint numbers) were significant at 3 months, but by 6 months no reductions in the mean DAS28 were observed. In fact, most patients reported the recurrence of pain and morning stiffness 3 months after the last infusion of pamidronate.

In contrast to pamidronate studies in ankylosing spondylitis,[26-28] use of pamidronate in rheumatoid arthritis had rapid onset of action which appeared before 3 months of treatment. Therefore, 3 consecutive monthly pamidronate infusions constituted a reasonable trial of therapy. In other words, if no response appears in 3 months, it is unlikely to get benefits from continuing the drug to control pain and inflammation. Patients who received 60 mg of pamidronate on a monthly ba-

sis for 3 consecutive months showed significant improvements in clinical outcomes. However, this was limited to the treatment period and shortly after it. Nevertheless, almost 40% of patients appeared to have a substantial clinical response, as shown by a 50% reduction in the DAS28.

Although previous studies have also shown a poor correlation between clinical indices of disease activity and levels of ESR and CRP in ankylosing spondylitis (AS),[27,29] we found a good correlation between clinical response and changes of acute phase reactants in rheumatoid arthritis. Results of previous work, however, suggest that pamidronate pulse therapy with more frequent infusions over a longer period of time may be more effective and may induce more prolonged suppression of disease activity.[17,18,25,30] Treatment with pamidronate consecutive monthly infusions was well-tolerated, with mild adverse events primarily confined to the first IV infusion.

CONCLUSION

The results of this study suggested that pamidronate may be effective in rheumatoid arthritis. It can thus be a choice for difficult cases of rheumatoid arthritis with severe pain and osteoporosis. Further multicenter placebo-controlled trials are nonetheless required to confirm our findings. Therefore, a trial of IV pamidronate therapy in patients with DMARDs refractory disease before using anti-tumor necrosis factor (TNF) or biologic therapies may constitute a reasonable treatment alternative.

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