

Case Report**Pamidronate infusion improved two cases of intractable seronegative rheumatoid arthritis***Mansour Salesi¹, Peyman Mottaghi²***Abstract**

Pamidronate is a bisphosphonate derivative that can inhibit bone resorption by actions on osteoclasts and increase bone density in spite of treatment with steroids. This drug has the anti-inflammatory effect by increase apoptosis of monocytes. 5-10 percent of rheumatoid arthritis patients is seronegative and may be resistant to conventional disease modifying anti rheumatic drugs (DMARDs). Intravenous (IV) pamidronate can be effective in disease control in seronegative rheumatoid arthritis. We report two cases of seronegative and drug resistant rheumatoid arthritis that favorably responds to pamidronate.

KEYWORDS: Pamidronate, Seronegative, Rheumatoid Arthritis.

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Pamidronate is a derivative bisphosphonate used for conditions such as hypercalcemia of malignancy, Paget's disease, osteolytic bone lesions, pediatric osteoporosis, osteogenesis imperfect, and prostate cancer.¹ It can inhibit bone resorption by impacting on osteoclasts. It also induces a rapid and sustained reduction in the serum level of biochemical markers of bone resorption and cartilage degradation.¹ Pamidronate therapy results in an increase of bone density regardless of treatment with steroids. This augments is associated with a suppression of interleukin-1 \square production in monocytes of the patients treated with pamidronate. This anti-inflammatory effect could be due to an increase in the apoptosis of monocytic cells.²

High titer of the rheumatoid factor is notable in serum of most of the patients with rheumatoid arthritis; however, 5-10 percent of the patients remain seronegative.³ Pamidronate infusion resulted in a rapid and persistent reduction in urinary calcium and hydroxyproline excretions. A single IV infusion

of pamidronate in patients with rheumatoid arthritis (RA) is safe, suppresses bone resorption, and can reduce the disease activity. It is suggested that the effect on disease activity is dose-dependent.⁴ Also, It is suggested that bones have complex sensory inner substance P, prostaglandin E₂, and calcitonin gene related peptide, which probably is influenced by bisphosphonate.⁵ When a patient with rheumatoid arthritis is resistant to conventional DMARDs, we usually start one of the anti-TNF agents such as Etanercept, Infliximab, or Adalimumab.⁶ A great number of patients in our country cannot afford these drugs. In this article, we report two severe intractable rheumatoid patients who dramatically respond to pamidronate; a cheap, safe and available drug that controlled disease activity and can be useful for osteoporosis of these patients.

Case 1

In Alzahra University Hospital of Isfahan, Iran, the a 42-year-old homemaker woman, who used to suffer from rheumatoid arthritis since

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Table 1. DAS28 and changes of its components during the pamidronate infusion courses (First case)

	Tender joint count	Swollen joint count	ESR	DAS28
Before the first pamidronate infusion	16	12	75	7.35
Before the second pamidronate infusion	5	3	30	4.61
Before the third pamidronate infusion	1	1	15	2.88
One month after the last infusion	0	1	11	2.03
Three months after the last infusion	2	1	20	3.31

DAS28: disease activity score of 28 joints

ESR: erythrocyte sedimentation rate

2004 was admitted. During this time, rheumatoid factor and anti-cyclic citrullinated peptide (anti-ccp) always had been negative. In this period, she had wrists, shoulders, knees, and ankles involvement, and never been improved completely.

The patient was under the treatment of oral Methotrexate (10 mg per week), Sulfasalazine (1500 mg/day), Diclofenac (50 mg/day), and low dose Prednisolone (7.5 mg/day). Dose escalation did not improve disease activity score of 28 joints (DAS28 > 5.1) and laboratory parameters.

She was admitted to the hospital due to refractory joints pain, tenderness, leukocytosis ($12 \times 10^3/\text{ul}$), and elevated ESR (65 mm/h) and CRP (42 mg/l). In addition, she received steroid pulses (IV methylprednisolone sodium succinate 500 milligram) during each admission. She was the candidate for biologic therapy, but she could not afford it. Due to this problem, we started 5 mg/kg of oral Cyclosporine-A for her.

After four weeks, she felt better, and tenderness decreased, but swelling continued. ESR (35 mm/h) and CRP (22 mg/l) improved slightly; but during this period, blood pressure and serum creatinine increased. We inevitably decrease cyclosporine dose to 3 mg/kg. Unfortunately, by tapering the drug dosage, the clinical and laboratory signs recurred. In respect of anti-inflammatory effect of pamidronate, after signing the inform consent by the patient, we decided to start single infusion of 60 mg drug for her. After four weeks, patient felt better and clinical and laboratory indices were improved. We continued 60mg infusions monthly

until three months. (In a 3-month period, patient received three infusions of 60mg pamidronate). After the second infusion, all the clinical and laboratory indices of the patient resolved completely. Joint tenderness improved dramatically and swelling also was decreased. ESR, CRP, and leukocytosis return to normal limit. Disease activity index decreased to less than 2.6 (DAS28 < 2.6) (Table 1).

By ameliorating of the joint tenderness and swelling, we discontinued cyclosporine and tapered other drugs gradually. After three months of the last drug injection, the disease was under control by 7.5 mg of oral methotrexate per week and 1 gram of oral Sulfasalazine per day. Laboratory and clinical indices of the disease activity were within the normal limits.

Case 2

In Alzahra University Hospital of Isfahan, a 23-year-old homemaker suffered from rheumatoid arthritis since 2007, was addmitted.

In the disease course, she had right wrist, elbows, shoulders, jaw, knees, and ankles involvement. In the laboratory examinations, she had a negative rheumatoid factor and anti-ccp, elevated ESR (87 mm/h) and CRP (45 mg/l), and leukocytosis ($13.4 \times 10^3/\text{ul}$). In the disease course, she was under the treatment of oral Methotrexate (10 mg/week), Sulfasalazine (2000 mg/day), Naproxen (500 mg/day), and prednisolone (7.5 mg/day). This patient, as the previous case, could not afford biologic drugs. In this regrad, we started oral cyclosporine A (3mg/kg) due to refractoriness to conventional

Table 2. DAS28 and changes of its components during the pamidronate infusion courses (Second case)

	Tender joint count	Swollen joint count	ESR	DAS28
Before the first pamidronate infusion	18	10	82	7.54
Before the second pamidronate infusion	6	4	38	4.83
Before the third pamidronate infusion	2	3	17	3.4
One month after the last infusion	0	1	12	2.16
Three months after the last infusion	1	1	21	3.18

DMARDs. We injected both knees by Triamcinolone in two intervals. After three weeks, patient felt better and disease activity index, ESR, CRP and leukocytosis improved.

However, after the dose reduction in each time, clinical and laboratory signs of disease relapsed. In this respect, after signing the inform consent by the patient, we decided to start intravenous pamidronate 60 mg per month until three months. After four weeks, laboratory and clinical signs of the patient decreased and after eight weeks, the entire patient's joint tenderness improved. Swelling disappeared in all joints except in one knee (Table 2).

Even so, we gradually started to tapered drugs. After 3 months of the last infusion, the patient only received one-gram oral Sulfasalazine per day and other drugs were discontinued.

Discussion

Rheumatoid arthritis is a disabling disease that

in some cases is refractory to conventional DMARDs. Rheumatoid factor is positive in most of the cases, but some cases are seronegative and resistant.³ Biologic drugs most commonly are used for refractory cases to conventional DMARDs,⁶ but they are expensive. Pamidronate is a cheap intravenous bisphosphonate that has some anti-inflammatory properties by increasing apoptosis of monocytes.² We reported two cases of severe seronegative RA that responded to this drug. By this report, we can schedule a more extensive research in this subject to identify the useful property of pamidronate.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

MS and PM carried out the design and coordinated the study, participated in data collection and prepared the manuscript. All authors have read and approved the content of the manuscript.

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