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Treatment of ankylosing spondylitis with pamidronate: an open label study

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Non-steroidal anti-inflammatory drugs (NSAIDs) and physiotherapy constitute the standard treatment for patients with ankylosing spondylitis (AS). Currently, there are no good disease modifying agents. Tumour necrosis factor antagonists, though effective, are very expensive and associated with an increased risk of infections. Pamidronate, an amino bisphosphonate is believed to have anti-inflammatory properties. We evaluated the role of pamidronate infusions in patients with AS refractory to NSAIDs.

Twenty one patients fulfilling modified New York criteria¹ for AS with active disease despite use of the maximal dose of two NSAIDs were recruited. Active peripheral arthritis and use of disease modifying antirheumatic drugs were reasons for exclusion. The mean (SD) age of the patients (male: female 20:1) was 31.6 (8.7) years and the mean (SD) disease duration 9.2 (5.5) years. The treatment regimen comprised monthly pamidronate infusions (60 mg over 4 hours) for 6 months. Patients were allowed to continue taking NSAIDs. Patients were assessed for response in the four Assessment in Ankylosing Spondylitis (ASAS) domains: Bath AS Functional Index (BASFI), pain on a visual analogue scale (VAS), patient global assessment VAS, and inflammation (morning stiffness—mean of items 5 and 6 of the Bath AS Disease Activity Index (BASDAI)).²

Fifteen patients completed all six infusions. Four were withdrawn owing to serious adverse effects. Two patients were excluded for protocol violation and loss to follow up, respectively. Figure 1 shows the effects of pamidronate on ASAS outcome domains among the patients completing all six infusions. None of the outcome measures improved significantly, although pain and global assessment showed a trend towards improvement (table 1).

The ASAS responses were analysed on an intention to treat basis. Only 4/21 (19%) patients achieved an ASAS 20

response and no one achieved an ASAS 40 response. In two patients the disease activity increased by more than 20% in all the four domains.

Maksymowych *et al* documented significant efficacy of pamidronate infusions in AS.^{3–5} Improvement in disease activity (BASDAI 25% reduction in 63% patients), function, global assessment, and metrology were seen at 6 months among patients receiving 60 mg pamidronate infusions.⁵ This corresponded to an ASAS 20 response of 60.2% in a post hoc analysis.⁶ Our patients had moderately active disease and we expected similar response rates. However, the 19% ASAS 20 response rate achieved was no different from the 25% expected in controls.⁷ None of the patients achieved an ASAS 40 response, considered to be a more robust tool. The results are more like those observed by Haibel *et al*, who

Figure 1 Effect of pamidronate infusions on ASAS domains for disease activity.

Table 1 Change in ASAS outcome domains

Outcome domain	Median (IQR)		p Value*
	Baseline	Six months	
BASFI	44.4 (60.8–22.3)	42.3 (53.3–34.4)	0.68
Pain VAS	58 (74–35)	47 (60.5–24.5)	0.09
Global assessment VAS	48 (77.5–32)	48 (61–30)	0.08
BASDAI morning stiffness	49 (63.3–27.5)	40 (45.5–25.3)	0.22

*Wilcoxon's matched pairs, signed ranks test.

documented a modest ASAS 20 response despite employing a more intensive regimen.⁸ Similarly, Cairns *et al* found only modest improvement in the BASDAI (6.8 to 5.75).⁹ A shorter disease duration (9.2 years present study *v* 15.1 years Maksymowych *et al*) as well as slightly lower disease activity cannot explain the observed lack of efficacy.

Adverse effects were seen in 16 patients, most of which were minor and well tolerated (post-infusion fever and myalgias in 12, mild uveitis in one). Three patients experienced serious adverse effects (renal disease in two, gastrointestinal problems in one) temporally related to the infusions. Renal adverse events included doubling of the serum creatinine levels and nephrotic range proteinuria, respectively. A relapsing form of glomerulopathy is a rare adverse effect of pamidronate infusions.¹⁰ Our patient did not consent to a renal biopsy, and the proteinuria gradually resolved. The third patient had severe diarrhoea and anorexia lasting for 2 months for which no alternative pathology could be found. One patient developed a severe disease flare after the third infusion (severe bilateral uveitis and peripheral arthritis requiring high dose steroid treatment). This patient had history of mild uveitis and peripheral arthritis 4 years ago. It cannot be ascertained whether pamidronate was responsible for the flare or this represented a lack of efficacy of the drug in this patient.

In conclusion, pamidronate infusions did not decrease disease activity significantly in patients with moderately active AS refractory to NSAIDs. The study raises questions about the efficacy of monthly pamidronate infusions as a treatment for AS.

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Glucocorticoid resistance in a girl with Takayasu's arteritis

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We report the case of a 16 year old girl with Takayasu's arteritis, which started with a bilateral neck pain associated with fever and a carotid murmur. A Doppler ultrasound of the neck showed a bilateral carotid involvement with thickened arterial walls and increased blood flow velocity, and a computed tomographic scan of the aorta showed involvement of the abdominal tract.

Treatment was started with oral prednisone and methotrexate, with a very poor clinical response (fig 1); acute phase reactants were significantly raised, recurrent fever persisted, and abdominal pain developed showing that the abdominal

aorta was affected. Treatment with intravenous boluses of high dose methylprednisolone gave transient benefit; treatment with glucocorticoids (GCs) was continued and additional immunosuppressant drugs were progressively added, still without any clinical and laboratory sign of remission. To confirm that the patient was taking her treatment, oral betamethasone was given under strict supervision during a period of admission in hospital, but still with no sign of clinical improvement. To obtain guaranteed steroid absorption, intravenous (IV) betamethasone was given in hospital for a 2 week period and for the following months at home, still without any benefit.