serum M-CSF. Additionally, significant correlations between M-CSF and activity index in patients with ankylosing spondylitis and rheumatoid arthritis also highlight the potential role of M-CSF in evaluating the activity of the two diseases.

Authors' affiliations
P-T Yang, W-G Xiao, L-J Zhao, Department of Rheumatology and Immunology, First Affiliated Hospital, China Medical University, Shenyang, People's Republic of China
H Kasai, L-M He, A Yamashita, X-W Deng, M Ito, Department of Microbiology, Interdisciplinary Graduate School of Medicine and Engineering, University of Yamanashi, Tamaho, Yamanashi, Japan

Competing interests: None declared.

Correspondence to: P-T Yang, Department of Rheumatology and Immunology, First Affiliated Hospital, China Medical University, Shenyang 110001, People's Republic of China; yangpingting@yahoo.com

Accepted 10 July 2006

REFERENCES

1 **Garrett S**, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Sponditis Disease Activity Index. *J Rheumatol* 1994;**21**:2286–91.
2 **Weinblatt ME**, Coblyn JS, Fox DA. Efficiency of low-dose methotrexate in rheumatoid arthritis. *New Engl J Med* 1985;**28**:818–22.
3 **Razzaque MS**, Foster CS, Ahamed AR. Role of enhanced expression of m-CSF in conjunctiva affected by cicatricial pemphigoid. *Invest Opthalmol Vis Sci* 2002;**43**:2977–83.
4 **Campbell IK**, Ianches G, Hamilton JA. Production of macrophage colony-stimulating factor (M-CSF) by human articular cartilages and chondrocytes: modulation by interleukin-1 and tumor necrosis factor alpha. *Biocbim Biophys Acta* 1993;**1182**:57–63.
5 **Braun J**, Bollow M, Neure L, Seipelt E, Seyrekbasan F, Herbst H, *et al*. Using of immunohistological and in situ hybridization techniques in the examination of sacroiliac joint biopsy specimens from patients with ankylosing spondylitis. *Arthritis Rheum* 1995;**38**:499–505.
6 **Yang C**, Gu J, Rihl M, Baeten D, Huang F, Zhao M, *et al*. Serum levels of matrix metalloproteinase 3 and macrophage colony-stimulating factor 1 correlate with disease activity in ankylosing spondylitis. *Arthritis Rheum* 2004;**51**:691–9.
7 **Koth K**. Structure-function studies on human macrophage colony-stimulating factor (M-CSF). *Mol Reprod Dev* 1997;**46**:31–8.

Cyclic intravenous pamidronate treatment in children with nodulosis, arthropathy and osteolysis syndrome

S M Al-Mayouf, S M Madi, B S Bin-Abbas

Ann Rheum Dis 2006;**65**:1672–1673. doi: 10.1136/ard.2005.035725

Nodulosis, arthropathy and osteolysis (NAO) syndrome is a rare autosomal recessive multicenteric osteolysis.[1 2] Few therapeutic studies have proved the efficacy of pamidronate in children with genetic osteoporotic syndrome such as osteogensis imperfecta.[3 4]

Therefore, we conducted an uncontrolled prospective study to assess the effect of cyclic intravenous pamidronate treatment on the clinical course of NAO syndrome in children and its effect on bone mineral density.

Seven children with NAO syndrome aged 5–14 years were treated with intravenous pamidronate between June 2003 and July 2004. The treatment was given after informed consent was obtained from the parents.

Pamidronate was diluted in 250 ml of isotonic saline and infused over a 4 h period on each of three consecutive days every 3 months for 1 year. The dose was 2 mg/kg/infusion. The patients were maintained on 800 IU/day vitamin D, and at least 800 mg/day of elemental calcium supplement. The patients had clinical and functional assessments using the Childhood Health Assessment Questionaire and the Visual Analogue Scale.[5]

All patients had normal serum levels of calcium, magnesium, phosphorus, alkaline phosphatase, parathyroid hormone, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, serum osteocalcin, urine spot for cross-linked N-telopeptide type I collagen (NTX), calcium, phosphorus and creatinine. *x* Rays of hands and feet, and bone mineral density (BMD) of the lumbar spine and the whole body, were assessed before and at the end of the treatment course. z Scores and the number of standard deviations (SD) for BMD above or below the mean for age-matched controls were derived on the basis of the manufacturer's data. The possible side effects were monitored.

The treatment was well tolerated by all patients. They reported a decrease in limb and joint pain and improvement in functional ability. However, it was not significant ($p < 0.094$; table 1). All patients had significant and progressive reduction in urinary NTX with treatment ($p < 0.01$), and low BMD in the lumbar spine ranging from 0.1 to 0.59 (mean (SD) 0.4 (0.18)) with z scores ranging from −2 to −5.5 (mean (SD) −3.25 (1.35)). At the end of treatment, the mean (SD) BMD increased significantly to 0.63 (0.04) ($p < 0.03$) and z scores to −1.08 (1.2) ($p < 0.03$). Increased mineralisation was observed on conventional *x* ray in one patient.

Idiopathic osteolysis is a rare skeletal disorder, with progressive bone destruction.[6–8] Recently, the mutational inactivation of matrix metalloproteinase-2 has been identified in patients with NAO syndrome, which represents the first hereditery deficiency of a metalloproteinase described in man.[2] Several studies have reported beneficial effects of bisphosphonate treatment in children with different genetic osteoporotic syndromes.[4 9 10] We treated seven patients with NAO using cyclic intravenous pamidronate, which resulted in

Table 1 Changes observed in patients with nodulosis, arthropathy and osteolysis during pamidronate treatment

	Before	After	p Value
Urinary NTX	550.57 (367)	252 (204)	0.01
Alkaline phosphatase	255.7 (163.1)	134.9 (36.6)	0.094
z Score lumbar BMD	−3.25 (1.35)	−1.08 (1.23)	0.03
z Score whole body BMD	−1.72 (1.57)	−1.18 (1.08)	0.08
VAS	1.3 (0.27)	0.77 (0.62)	0.06
CHAQ	1.73 (1.0)	1.29 (0.76)	0.094

BMD, bone mineral density; CHAQ, Childhood Health Assessment Questionnaire; NTX, cross-linked N-telopeptide type I collagen; VAS, Visual Analogue Scale.
Values are mean (SD).

progressive reduction in urinary excretion of NTX, resulting from an improvement in the bone resorption. However, there was no significant change in alkaline phosphatase or osteocalcin levels. The z score of the lumbar spine improved significantly over the treatment period, suggesting an improvement in BMD, which may reflect an improvement in the balance between bone formation and resorption. We believe that these patients require an intensive and prolonged course of treatment, and a close follow-up that will help delineate the beneficial effect of the treatment.

Authors' affiliations
S M Al-Mayouf, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
S M Madi, Department of physiotherapy, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
B S Bin-Abbas, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Competing interests: None declared.

Correspondence to: S M Al-Mayouf, Department of Pediatrics, King Faisal Specialist Hospital and Research Center, PO Box 3354 (MBC-58), Riyadh 11211, Saudi Arabia; mayouf@kfshrc.edu.sa

Accepted 15 May 2006

REFERENCES

1 **Al-Mayouf S**, Majeed M, Hugosson C, Bahabri S. New form of idiopathic osteolysis: nodulosis, arthropathy and osteolysis (NAO) syndrome. *Am J Med Genet* 2000;**93**:5–10.
2 **Martignetti J**, Aqeel A, Sewairi W, Boumch C, Kambouris M, Al-Mayouf SM, *et al*. Mutation of the matrix metalloproteinase 2 gene (MMP2) causes a multicentric osteolysis and arthritis syndrome. *Nat Genet* 2001;**28**:261–5.
3 **Glorieux F**, Bishop N, Plotkin H, Chabot G, Lanoue G, Travers R. Cyclic administration of pamidronate in children with severe osteogenesis imperfecta. *N Engl J Med* 1998;**339**:947–52.
4 **Lala R**, Matarazzo P, Bertelloni S, Buzi F, Rigon F, de Sanctis C. Pamidronate treatment of bone fibrous dysplasia in nine children with McCune-Albright syndrome. *Acta Paediatr* 2000;**89**:188–93.
5 **Madi S**, Al-Mayouf SM, Gainger C, Bahabri S. The arabic version of childhood health assessment questionnaire modified for arabic children. *Saudi Med J* 2004;**25**:83–7.
6 **Pai G**, Macpherson R. Idiopathic multicentric osteolysis: report of two new cases and review of the literature. *Am J Med Genet* 1988;**29**:929–36.
7 **Petit P**, Fryns J. Distal osteolysis, short stature, mental retardation and characteristics of facial appearance: delineation of an autosomal recessive subtype of essential osteolysis. *Am J Med Genet* 1986;**25**:537–41.
8 **Eisenstein D**, Poznanski A, Pachman L. Torg osteolysis syndrome. *Am J Med Genet* 1998;**80**:207–12.
9 **Bianchi M**, Cimaz R, Bardare M, Zulian F, Leopre L, Boncompagni A, *et al*. Efficacy and safety of alendronate for the treatment of osteoporosis in diffuse connective tissue diseases in children: a prospective multicenter study. *Arthritis Rheum* 2000;**43**:1960–6.
10 **Lepore L**, Pennesi M, Barbi E, Pozzi R. Treatment and prevention of osteoporosis in juvenile chronic arthritis with disodium clodronate. *Clin Exp Rheumatol* 1991;**9**(Suppl 6):33–5.

Correlation of oestrogen receptor gene polymorphism with gouty arthritis

C-M Huang, S-F Lo, H-C Lin, M-L Chen, C-H Tsai, F-J Tsai

Ann Rheum Dis 2006;**65**:1673–1674. doi: 10.1136/ard.2005.051375

Gout represents a group of diseases characterised by hyperuricaemia, arthritis, and uric acid crystal formation. Men have a higher level of serum uric acid and are more susceptible to gout than women. The lower serum urate values in women of reproductive age compared with their male counterparts have been ascribed to lower renal postsecretory uric acid reabsorption.[1] An increase in ratios of testosterone to oestradiol has been reported to be associated with hyperuricaemia.[2]

The oestrogen receptor gene is located at chromosome 6q25.1 and has a thymine–adenine (TA) dinucleotide repeat polymorphism 1174 bp upstream from exon 1. This polymorphism has been shown to be associated with menopausal osteoporosis,[3] coronary artery disease[4] and rheumatoid arthritis.[5] The androgen receptor has three main functional domains that are located at Xq11–12, near the centromere of the X chromosome. Binding of the androgen receptor–androgen complex activates the expression of other genes (transactivation). This transactivation activity depends on the transactivation domain of the protein encoded by exon 1, which contains a polymorphic CAG repeat sequence. Previous studies have shown that the CAG repeat is associated with inflammatory arthritis, such as rheumatoid arthritis[6] and ankylosing spondylitis,[7] and severity of coronary artery disease in men.[8]

METHODS AND RESULTS

In this study, we enrolled 196 patients (181 men and 15 women) with gout according to the 1977 revised American College of Rheumatology criteria.[9] In addition, 102 unrelated, healthy people (57 men and 45 women) living in central Taiwan served as control subjects. Informed consent was obtained from all subjects who participated in this study. Genomic DNA was prepared from peripheral blood using a genomic DNA isolation reagent kit (Genomarker, Taipei, Taiwan). The oestrogen receptor gene TA repeats and androgen receptor gene CAG repeats in patients and controls were typed by polymerase chain reaction.

The frequency distribution of the oestrogen receptor gene polymorphism in patients with gouty arthritis and healthy controls is presented in fig 1. Patients with gout had significantly shorter oestrogen receptor gene TA repeats than their sex-matched controls (men: mean 14.9 *v* 17.2, $p<0.001$; women: mean 14.8 *v* 17.0, $p = 0.002$; table 1). We further classified the patients and controls into groups with shorter TA repeats ($\leqslant 18$) and longer TA repeats (>18 repeats). The frequency of the shorter TA repeats ($\leqslant 18$) was considerably higher in patients with gout than in healthy controls (data not shown).

DISCUSSION

Our findings suggest that the oestrogen receptor gene TA repeat polymorphism is associated with the risk of developing gout in both men and women. In men, the risk is more consistently correlated with decreasing length of TA repeats. The protective effect of long TA repeats increases dramatically as the frequency of TA repeats increases in men. On the basis of the reports mentioned earlier, we conjecture that longer oestrogen receptor gene TA repeats increase the transactivational activity of the oestrogen receptor, facilitating uric acid excretion and thereby decreasing the susceptibility to gout. However, the speculation will need to be confirmed by further studies.