



Allergologia et immunopathologia

Sociedad Española de Inmunología Clínica,
Alergología y Asma Pediátrica

www.elsevier.es/ai



RESEARCH LETTER

Efficacy of treatment with IL-1RA in Majeed syndrome



Introduction

Auto-inflammatory syndromes are primary immunodeficiencies characterised by spontaneous and recurrent systemic inflammation episodes without an underlying infectious, neoplastic or autoimmune origin. These diseases are little known, and are therefore underdiagnosed.

One such disorder is Majeed syndrome,⁵ a rare autosomal recessive disease manifesting as early-onset chronic recurrent multifocal osteomyelitis (CRMO)^{2,7–10} with haematological alterations (dyserythropoietic microcytic anaemia), and which is sometimes also accompanied by recurrent fever or neutrophilic dermatosis. The syndrome is caused by homozygous mutations of the LPIN2 gene located on chromosome 18p.^{3,4}

Children with Majeed syndrome^{5,6} suffer recurrent joint pain sometimes accompanied by fever, and with radiological findings indistinguishable from those of infectious osteomyelitis. However, the bone marrow biopsy cultures are sterile, and antibiotic treatment therefore does not lead to improvement. Analgesics and corticosteroids are partially effective. The disease evolves towards persistent joint inflammation with secondary contractures and deformities, and important functional disability.

Interleukin-1 receptor antagonists (IL-1RA) have been prescribed to treat some auto-inflammatory syndromes, although there is little experience on their use in children with Majeed syndrome.¹ Two cases have been reported to date, with satisfactory results following the administration of IL-1RA¹ – this supporting the idea that IL-1 dysregulation might play an important role in the pathogenesis of the syndrome.

Clinical case

A 13-year-old boy presented with a history of macrocephalia, low body height, speech and learning retardation, attention deficit disorder and alpha-thalassemia minor. From six years of age he suffered recurrent episodes of pain and spontaneous swelling of the small and medium-sized joints (ankle, dorsal region, heel and big toe of both feet,

wrists and elbows) and functional impotency, with no fever, intercurrent infection or clear triggering factor.

At 10 years of age he was evaluated in the Department of Paediatrics of our hospital, including a whole-body and left foot MRI scan (Figs. 1–4) and a CT-guided left calcaneal bone biopsy with bone marrow aspiration. An infectious or neoplastic origin was discarded, and chronic recurrent multifocal osteomyelitis (CRMO) was diagnosed.^{2,7–10} Bisphosphonates (pamidronate), nonsteroidal anti-inflammatory drugs, corticosteroids and potent opioid analgesics (Fig. 5) proved scanty effective, and the patient required frequent hospital admissions for morphic drug perfusion.

In May 2013, at 12 years of age, he was seen in the Section of Paediatric Immunology, where a clinical evaluation and thorough immunological study were carried out – the only alteration to highlight being acute phase reactant elevation during the disease flare-ups (erythrocyte sedimentation rate (ESR) up to 70 mm and C-reactive protein up to 5.9 mg/dl) (Fig. 5). The immunological study (immunoglobulins, complement and lymphocyte subpopulations) only evidenced a polyclonal IgG increment, and the genetic analysis revealed mutation of the LPIN2 gene in exon 17 (c.2327+1G-C).^{3,4}

The patient was receiving third-step analgesia (WHO analgesia scale), with a progressive increase in medication requirements, increasingly frequent flare-ups (four admissions in the previous six months), and with a strong negative impact upon quality of life and family environment.

With the suspicion of Majeed syndrome,^{5,6} in June 2013 treatment was started with recombinant IL-1RA (Anakinra) in the Day Hospital, at a dose of 1 mg/kg b.w. every 24 h via the subcutaneous route¹, with an excellent response allowing suspension of the analgesic treatment within two weeks. The patient has remained free of symptoms to date (Fig. 5).

Comment

We have presented the case of a boy with a variant of chronic recurrent multifocal osteomyelitis (CRMO) – Majeed syndrome^{5,6} – refractory to analgesic and anti-inflammatory treatment (including potent opioids), with a strong impact upon the patient's quality of life, which showed a very good response to IL-1RA treatment.¹

Since the firm diagnosis was established and treatment was started, there have been no further flare-ups, and the patient has required no further hospital admissions or



Figures 1–4 T2W MRI scan of the left foot with fat suppression (STIR) and T1W knee and leg scan. Important replacement of the normal adipose marrow component with nodular images (hypointense in T1W and hyperintense in T2W sequencing with STIR), particularly apparent in the metacarpal region, astragalus, calcaneus, scaphoid bone, both tibiae and fibulae, and both femurs – with no radiological evidence of aggressive behaviour. These findings would be consistent with proliferative/dysplastic disease, though other more infrequent disorders such as multifocal osteomyelitis or non-Langerhans cell histiocytosis (Erdheim-Chester disease) cannot be discarded.

	Before IL-1RA Therapy	Six months after il-1RA therapy
C-reactive protein	5.9 mg/dl	1.2 mg/dl
ESR	70 mm	34 mm
Symptoms	Frequent episodes of intense pain and swelling of the ankles, dorsal region, heel and big toe of both feet, wrists and elbows	Asymptomatic
Treatment	Bisphosphonates (pamidronate), nonsteroidal antiinflammatory drugs, corticosteroids, potent opioids (morphine, oxycodone, fentanyl)	Recombinant IL-1RA (Anakinra) s.c. on a daily basis

Figure 5 Acute phase reactants, symptoms and treatments before and six months after the start of IL-1RA therapy.

analgesia. He has been able to lead a normal life for a boy of his age. We thus suggest that IL-1RA treatment could be an alternative for patients with CRMO refractory to conventional therapies.^{1,7–10} Likewise, the results obtained support the idea (suggested by other studies) that IL-1 dysregulation

might play an important role in the pathogenesis of the syndrome.¹

It can be concluded that in the event of symptoms similar to those described herein, paediatricians should consider this immune disease among the possible diagnoses.

References

1. Herlin T, Fiirgaard B, Bjerre M. Efficacy of anti-IL-1 treatment in Majeed syndrome. *Ann Rheum Dis.* 2013;72:410–3.
 2. Hedrich M. Aseptic bone inflammation SP0039 Immunological and genetic basis of CRMOC. *Ann Rheum Dis.* 2013;71 Suppl. 3:10.
 3. Al-Mosawi ZS, Al-Saad KK, Ijadi-Maghsoodi R. A splice site mutation confirms the role of LPIN2 in Majeed syndrome. *Arthritis Rheum.* 2007;56:960–4.
 4. Ferguson PJ, Chen S, Tayeh MK, Ochoa L, Leal SM, Pelet A, et al. Homozygous mutations in LPIN2 are responsible for the syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia (Majeed syndrome). *J Med Genet.* 2005;42:551–7.
 5. Majeed HA, Al-Tarawna M, El-Shanti H, Kamel B, Al-Khalaileh F. The syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia: report of a new family and a review. *Eur J Pediatr.* 2001;160:705–10.
 6. Majeed HA, El-Shanti H, Al-Rimawi H, Al-Masri N. On mice and men: an autosomal recessive syndrome of chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anaemia. *J Pediatr.* 2000;137:441–2.
 7. Girschick HJ, Raab P, Surbaum S, Trusen A, Kirschner S, Schneider P, et al. Chronic non-bacterial osteomyelitis in children. *Ann Rheum Dis.* 2005;64:279–85.
 8. Jansson A, Renner ED, Ramser J, Mayer A, Haban M, Meindl A, et al. Classification of non-bacterial osteitis: retrospective study of clinical, immunological and genetic aspects in 89 patients. *Rheumatology (Oxford).* 2006.
 9. Jurik AG. Chronic recurrent multifocal osteomyelitis. *Semin Musculoskelet Radiol.* 2004;8:243–53.
 10. Huber AM, Lam PY, Duffy CM, Yeung RS, Ditchfield M, Laxer D, et al. Chronic recurrent multifocal osteomyelitis: clinical outcomes after more than five years of follow-up. *J Pediatr.* 2002;141:198–203.
- C. Pinto-Fernández^{a,*}, M.E. Seoane-Reula^{a,b}
- ^a *Department of Allergology, Gregorio Marañón University Hospital, Madrid, Spain*
^b *Section of Pediatric Immunology, Gregorio Marañón Maternal-Children's Hospital, Madrid, Spain*
- *Corresponding author.
E-mail address: celiapintofdez@yahoo.es
(C. Pinto-Fernández).