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# Letters to the Editor

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## Successful treatment with canakinumab of a paediatric patient with resistant Behçet's disease

Sir, Behçet's disease (BD) is a systemic vasculitis characterized by a wide clinical spectrum including recurrent oral and genital ulceration, uveitis, vascular, neurological, articular, renal and gastrointestinal manifestations [1]. Treatment of BD depends on the clinical manifestation and organ involvement. Although colchicine, NSAIDs and topical steroids are often sufficient for mucocutaneous and joint involvement, a more aggressive approach with immunosuppressive drugs is necessary for severe manifestations such as posterior uveitis, retinal vasculitis, recurrent fevers, vascular, neurological and gastrointestinal involvement. However, some patients still have refractory disease, flares or irreversible organ damage. Recent advances in the study of pathogenic mechanisms have enabled the identification of new potential targets and future biologic therapies for BD. In contrast to current non-specific immunosuppressive agents, often used empirically, the emergence of biotherapies provides the possibility of interfering with specific pathogenic pathways and appears to promise treatments for patients with refractory or relapsing BD [1].

We describe a child with juvenile BD with recurrent fevers, oral and genital ulceration, skin lesions, arthralgia and abdominal pain, who was unsuccessfully treated with a range of immunosuppressive drugs and biotherapies. He achieved clinical remission only with canakinumab, a fully human anti-IL-1 β antibody.

A 9-year-old Caucasian boy was diagnosed as having BD at the age of 5 years, based on typical clinical manifestations. When he was 2 years old, he had started to complain of constipation, abdominal pain and encopresis, associated with recurrent oral ulceration, skin lesions (papulopustolar with ulcers, especially on the face) and photophobia. Two years later he presented with recurrent fevers, genital ulceration and headaches. Laboratory tests showed mild anaemia (haemoglobin 11.7 g/dl), normal ESR and CRP level, and positivity for HLA-B51. Coeliac disease screening, ANA, ANCA, anti-*Saccharomyces cerevisiae* antibodies, aCL, anti-β2-glycoprotein antibodies and faecal calprotectin were all negative. A barium enema showed dolichocolon and diffuse hypokynesia of the large bowel. Gastrointestinal endoscopy and brain MRI were normal. A pathergy test was also performed and resulted positive after 48 h. Uveitis was excluded by ophthalmological examination.

A diagnosis of BD was made in October 2010 and treatment with colchicine (initially at the dosage of 0.25 mg/day, after 4 months increased to 0.5 mg/day) and prednisone 15 mg/day was commenced. After a few months, due to persistent oral and skin ulceration, associated with constipation, abdominal pain, arthralgia, recurrent fever and headache, the colchicine was interrupted and thalidomide 50 mg/day was added to the prednisone (0.5 mg/kg/day). Three months later, clinical symptoms were still present, so MMF 250 mg twice a day was substituted for the thalidomide. However, clinical improvement was still not reached after another 4 months; therefore, biotherapy with adalimumab (24 mg/m$^2$ every 2 weeks) was started in association with the MMF. Quite quickly, the fever, headache, abdominal pain and oral ulceration disappeared, but after a few months all systemic clinical features reappeared. So, adalimumab and MMF were stopped and anakinra (2 mg/kg) was introduced, initially at the dosage of 2 mg/kg/day, increased to 4 mg/kg/day, with only partial benefit. Oral and skin ulceration, recurrent fever, arthralgia, headaches and abdominal pain were in fact still present, associated with a persistent increase in inflammatory markers and mild anaemia. Thus, after 19 months of treatment with anakinra we switched to canakinumab, at a dose of 4 mg/kg every 28 days.

After 4 months of this therapy, complete clinical and laboratory remission was obtained. Of note, steroid treatment was gradually reduced to 5 mg/day. At the last follow-up (6 months after the first dose) the boy was completely asymptomatic.

BD is often difficult to treat, and requires biologic treatment in cases with severe systemic involvement. Initially, TNF inhibitor was used successfully, but resistant cases exist and hence other biologics have been tried. Canakinumab is a human mAb targeted at IL-1β that has been shown to be effective in various autoinflammatory syndromes such as cryopyrin-associated periodic syndrome and systemic JIA [2, 3]. Anakinra, a recombinant, non-glycosylated human IL-1 receptor antagonist, has been used in patients with BD refractory to conventional treatments [4]; and gevokizumab, a recombinant humanized anti-IL-1β antibody, was used in seven BD patients with resistant uveitis and retinal vasculitis [5]. Interestingly, our patient did not respond to anakinra, but benefited from canakinumab. Both agents are IL-1 blockers, but anakinra blocks IL-1α and IL-1β and has a short half-life (4–6 h), while canakinumab specifically targets IL-1β and has a longer half-life. To our knowledge, there are only a few published reports of BD patients treated with canakinumab: three adults [6, 7] and a 16-year-old girl [8].

To our knowledge our case is, therefore, the youngest reported so far. Although more studies are necessary to confirm the efficacy and safety of canakinumab in paediatric patients with persistent systemic

features, we think that canakinumab may be effective in the treatment of refractory BD and that a clinical trial is warranted.

**Rheumatology key message**

- Canakinumab can be effective in paediatric patients with refractory Behçet's disease.

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## Comment on: The validation of a diagnostic rule for gout without joint fluid analysis: a prospective study

Sir, Ideally, diagnosing a disease implies recognizing its possibility under all the forms in which it can present; being able to distinguish it from other diseases that can share a similar presentation; and also ascertaining that all diagnoses are correct. Fortunately this is possible in gout, a disease resulting from the deposition of MSU crystals in the surface of the articular cartilage and other tissues. The crystals are easily identifiable by microscopy in the SF of joints stricken by gout attacks and also in asymptomatic joints previously inflamed [1] if the patient has not been treated with urate-lowering drugs; also the crystals can be detected by needling a tophus. Although US is not yet at the level of providing an accurate diagnosis it allows the location of crystal aggregates or inflammation in joints less suitable for blind arthrocentesis, thus allowing them to be sampled for crystal analysis. In a proper setting, unequivocal gout diagnosis appears to be always possible with few exceptions.

It is against this background that Kienhorst *et al*. [2] published in *Rheumatology* a clinical diagnostic tool for gout. In a recent editorial [3] we highlighted the shortcomings of this approach for gout diagnosis, the key messages being that clinical recognition relies on the clinical skills and interests of the diagnosing physician, which allow him or her to properly interpret the clinical features encountered; diagnostic rules built mainly on typical features will hamper the detection of those not included in these features; and the purpose of the developed criteria should be clearly stated to avoid their use in settings different from that for which they were built.

Gout diagnosis and management by general physicians and even by rheumatologists is still far from optimal [4], and a diagnosis based on crystal identification remains underused and substituted by clinical approaches. Even the landmark clinical manifestation of gout—podagra—can result from other conditions such calcium pyrophosphate crystals, PsA or local problems when arthrocentesis is applied [5]. In the study by Kienhorst *et al*. [2] only patients with acute monoarthritis were enrolled to validate their tool. The authors felt confident that this tool would also work well for patients with oligo or polyarthritis, but—as they discuss—did not test it. The absence of crystal-proven series of gout means the exact frequency of patients with less characteristic clinical features is ignored and for sure, approaches such as the one developed by Kienhorst *et al*. [2] contribute to sustaining the idea of gout as a disease restricted to its paradigmatic clinical features. The 2007 EULAR recommendations [6] outline that 'For typical presentations of gout (such as recurrent podagra with hyperuricaemia) a clinical diagnosis alone is reasonably accurate but not