

Successful use of canakinumab in a patient with resistant Behçet's disease

Sirs,

Behçet's disease (BD) is a chronic, relapsing, multi-system inflammatory disorder clinically characterised by recurrent oral and genital ulcers, cutaneous lesions and uveitis (1). Other possible manifestations include arthritis, a positive pathergy test, thrombophlebitis, central nervous system disease and gastrointestinal ulcerations. It is generally not a life-threatening disease, although mortality can be associated with vascular-thrombotic manifestation, especially at a neurological level (2). In 1990, an International Study Group published a set of Criteria to facilitate the diagnosis of BD (1). According to this Criteria, the diagnosis must be considered when the patient presents recurrent oral ulcers and two other of the following features: recurrent genital ulceration, eye lesions, skin lesions and a positive pathergy test. There have been few randomised, controlled clinical trials regarding BD, and treatment is currently symptomatic and empirical, and is tailored according to the severity of clinical manifestations (3). Although the mechanisms underlying BD remain unknown and although the presence of clinical clusters indicates that several pathways might be involved, interleukin (IL)-1 seems to play a relevant role to its pathogenesis (4). Furthermore, IL-1 inhibition with anakinra recently proved successful in treating resistant BD patients, thus strengthening this hypothesis (5). We report herein the first resistant BD patient successfully treated with canakinumab, a fully human anti-interleukin (IL)-1 β monoclonal antibody.

A 20-year-old Caucasian female was admitted to our Unit with a 10-year history of recurrent oral and genital aphthosis, skin lesions (erythema nodosum and pseudo-folliculitis), arthritis mainly involving the knees, ankles and wrists, abdominal pain and headache. In addition to the clinical manifestations consistent with BD the patient also showed a granuloma annulare on the right hand.

The patient also referred recurrent prolonged fever episodes. Laboratory investigation during admission showed neutrophilic leukocytosis $27.89 \times 10^3/\text{mm}^3$, ESR 120 mm/h (n.v. <35), C-reactive protein (CRP) 14.84 mg/dl (n.v. <0.5), fibrinogen 689 mg/dl (n.v. <400), and serum amyloid A (SAA) 482 mg/L (n.v. <10). Kidney and liver function tests were normal. Ophthalmological and neurological evaluations were normal. Brain magnetic resonance image (MRI) study was negative. Colonoscopy revealed mild to moderate non-specific mucosal inflammation and multiple ulcers in the ileocolic region. The patient was investigated for mutations in the genes responsible for the most common hereditary periodic fever syndromes, such as the *MEFV*, *TNFRSF1A*, *NLRP3* and *MVK* genes. No mutations were found. The patient fulfilled the International

Study Group criteria and was diagnosed with BD (1). The HLA-B51 allele was positive. She had previously been treated with high-dose oral prednisone (1–1.5 mg/kg/daily), but every attempt to taper the corticosteroid dosage was followed by a disease relapse. Over the 10 years of active disease, she had also been treated with sulfasalazine up to 40 mg/kg/daily, methotrexate up to 15 mg/m² weekly, cyclosporine A 4–5 mg/kg/daily, azathioprine 3–4 mg/kg/daily and leflunomide 20 mg/daily. All these treatments failed to induce either an adequate clinical remission of disease or a normalisation of acute phase reactants, which were persistently elevated. The patient had subsequently been administered etanercept, a fusion protein of the tumor necrosis factor (TNF) receptor and the Fc domain of immunoglobulin G1 (IgG1), which was later withdrawn due to adverse reactions (recurrent urinary tract infections and bacterial endocarditis), as well as infliximab (which also caused recurrent urinary tract infections), a chimeric mouse-human monoclonal antibody against TNF- α . The patient's SAA levels also remained elevated during anti-TNF- α treatment. The subcutaneous IL-1 receptor antagonist Anakinra (100 mg/daily) was then started, and led to a remarkable clinical improvement and a decrease in SAA concentration to normal values. Unfortunately, its administration was interrupted a few weeks after the start of treatment, due to the onset of diffuse pruritic urticarial lesions of increasing severity. Subcutaneous canakinumab, the human anti-IL-1 β monoclonal antibody for the treatment of cryopyrin-associated periodic syndromes, was prescribed at a dose of 150 mg every 8 weeks, and proved efficacious in achieving a prompt and complete disease response without evidence of any adverse events. At 6-month follow-up, the patient was fever- and symptom-free, and SAA concentration (checked monthly for 6 months) remained stable within the normal range.

To date, the mainstay of BD therapy has been corticosteroids combined with colchicines. Immunomodulating drugs (methotrexate, azathioprine, chlorambucil and cyclophosphamide) can be employed in refractory patients or to taper glucocorticoids, while sulfasalazine is useful in cases of gastrointestinal manifestations (3). Interferon- α and anti TNF- α agents have also been administered successfully (6–9). Recently, IL-1 β inhibition proved successful both on eye (gevokizumab, 7 patients) (10) and central nervous system (anakinra, 1 patient) (5) involvement, thus strengthening the concept that BD is an IL-1-mediated disease (4). The safety, pharmacokinetics and clinical activity of gevokizumab (0.3 mg/kg), a recombinant humanised anti-IL-1 β antibody, have recently been evaluated in BD patients with resistant uveitis. The treatment induced a rapid and lasting clinical response in all subjects, with complete resolution of intraocular inflammation within 4–21 days (median 14 days) (10). To the best of our knowledge, no data exist regarding the effects of canakinumab on BD. Canakinumab is a fully hu-

man IgG1 anti-IL-1 β monoclonal antibody that binds to human IL-1 β with high specificity and neutralises this cytokine's bioactivity. In our patient, it proved to be effective both in bringing about a rapid and complete resolution of BD clinical manifestations and in normalising all markers of inflammation within a few weeks after the start of treatment. Moreover, the treatment was well-tolerated, and at the 6-month follow-up no adverse events were noted. Although promising, the results obtained with IL-1 antagonists are, to date, limited to a very few cases and must be further evaluated in larger cohorts of patients. Nonetheless, we suggest that canakinumab may be a successful treatment option for resistant BD.

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