International Journal of Dermatology

Case report

Long-term efficacy and safety of anakinra in a patient with Behçet's disease and concomitant tuberculosis infection

Giacomo Emmi[1,2,*], MD, Elena Silvestri[1,2,*], MD, PhD, Danilo Squatrito[1], MD, Antonio Vitale[3], MD, Daniela Bacherini[4], MD, Lorenzo Vannozzi[4], MD, Lorenzo Emmi[1], MD, Mario Milco D'Elios[1,2], MD, PhD, Luca Cantarini[3], MD, PhD, and Domenico Prisco[1,2], MD

[1]Department of Experimental and Clinical Medicine, University of Florence, [2]Interdisciplinary Internal Medicine, Center for Autoimmune Systemic Diseases, Behçet Center and Lupus Clinic, AOU Careggi, [3]Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Policlinico Le Scotte, University of Siena, Siena, and [4]Department of Translational Surgery and Medicine, Eye Clinic, University of Florence, Florence, Italy

Correspondence
Giacomo Emmi, MD
Department of Experimental and Clinical Medicine, University of Florence
Florence
Italy
E-mail: giacomaci@yahoo.it

*These authors contributed equally to the preparation of the manuscript.

Conflicts of interest: None.

Introduction

Behçet's disease (BD) is a systemic vasculitis with mucocutaneous, gastrointestinal, ocular, vascular, and neurological involvement.[1] Ocular manifestations represent one of major organ involvement, with a high rate of recurrences potentially resulting in partial or total blindness. Treatments may range from the topical approach to disease-modifying antirheumatic drugs and biological agents.[1] Tumor necrosis factor (TNF)-α inhibitors and interferon-α are usually effective in the majority of patients with severe ocular disease.[1]

Recent clinical observations with the interleukin (IL)-1 inhibiting agents anakinra,[2] canakinumab,[3–5] and gevokizumab[6] have suggested their potential role in the treatment of refractory Behçet's uveitis. Accordingly, in a multicenter retrospective study, we found that treatment with anakinra and canakinumab was effective and safe in 30 patients with BD, with an overall acceptable retention on treatment.[7]

Unlike anti-TNFα treatment, IL-1 inhibition has shown a good safety profile regarding the risk of severe infections, particularly in relation to tuberculosis (TB) reactivation.[8] Indeed, interfering with the IL-1 pathway seems safer in comparison with blocking TNFα. This consideration is relevant for patients with BD because of the high prevalence of this disease in geographical areas where TB is a social concern.[8]

In this regard, we report herein a patient with BD with concomitant latent TB infection successfully treated with anakinra as first-line biological therapy.

A 41-year-old man was diagnosed with BD in 2008 based on recurrent oral aphthosis, genital ulcerations, and pseudofolliculitis. His medical history was also relevant for monthly fever attacks, spontaneously resolved 1 year after the onset of symptoms, hip arthralgia, and

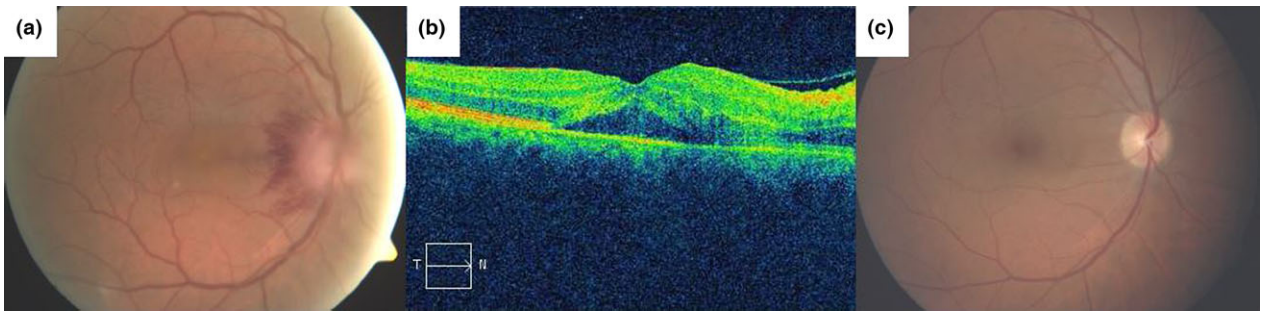

Figure 1 Ocular involvement before and at 12-month follow-up during anakinra treatment: (a) color fundus photograph showing optic disc swelling, peripapillary retinal edema, and hemorrhages in papillitis; (b) optical coherence tomography demonstrating serous foveal and interpapillomacular retinal neuroepithelial detachment; (c) color fundus photograph confirming complete resolution of the papillitis after 12 months of anakinra treatment

abdominal pain with diarrhea without evidence of inflammatory lesions at colonoscopy. No mutations in the *MEFV* gene, responsible for familial Mediterranean fever, were detected. BD symptoms were controlled with colchicine 1 mg/d until February 2014, when a bilateral anterior non-granulomatous uveitis occurred. Although on prednisone 1 mg/kg per day, in March 2014 the patient was admitted to our unit for continuous fever, recurrent oral ulcerations, and progressive worsening vision in the right eye. The ophthalmological evaluation revealed acute papillitis and a best-corrected visual acuity (BCVA) of 20/400 in the right eye, while the left eye was normal. Laboratory examinations, abdominal ultrasound, and a chest computed tomography did not show abnormalities. The Quantiferon test was positive. Treatment with corticosteroids (6-methylprednisolone 500 mg/d intravenously for 3 consecutive days followed by shortly tapering oral prednisone until 5 mg/d) and anakinra (100 mg/d subcutaneously) was started. Of note, no other disease-modifying antirheumatic drugs were used before starting anakinra. Despite the use of high-dose corticosteroids and anakinra, anti-TB prophylaxis was not administered because of proven multiple intolerance to anti-TB drugs; in particular, isoniazid and rifampicin were early interrupted due to gastrointestinal (nausea and vomit) and cutaneous (generalized urticaria) manifestations. A good clinical response was rapidly achieved, and the ophthalmologic evaluation performed 7 days after starting the treatment showed a dramatic visual improvement and a marked reduction of the optic nerve head swelling. Further ophthalmological evaluations performed every 2 months highlighted resolution of papillitis, increase of BCVA to 20/25, and absence of ocular inflammation during the following 12 months (Fig. 1). Anakinra treatment was well tolerated, and no adverse events or signs of TB reactivation occurred.

Anti-IL-1 agents are emerging as an important therapeutic option in BD,[2–7] with a good safety profile.[9] IL-1 is a proinflammatory cytokine secreted by a wide number of cell types, and increased levels of IL-1 play a major role in several disorders including autoinflammatory diseases.[10,11] In this regard, BD shows several clinical findings overlapping with those of autoinflammatory diseases;[12] moreover, polymorphisms in the IL-1-related genes have proven to confer susceptibility to BD.[13] Interestingly, recent data have shown that IL-1β from peptidoglycan/lipopolysaccharide-induced monocytes is significantly increased in patients with BD with active uveitis, thus providing a pathophysiological rationale for anti-IL-1 treatment in Behçet's uveitis.[14]

Noteworthy, our patient presented a positive Quantiferon-TB test, thus deserving some attention when starting anti-TNFα treatment. In fact, the risk of TB reactivation when using anti-TNFα agents represents a hot issue particularly in those areas where the infection is endemic, such as along the ancient Silk Road, where BD has a high prevalence and TB is a socioeconomic burden. Conversely, IL-1 inhibitors have shown a better safety profile than anti-TNFα regarding the risk of TB reactivation.[8]

Our report suggests that anakinra should not be reserved only to refractory patients with BD but highlights that in selected BD cases it should be taken into consideration also as a first-line biologic drug. This might be relevant particularly when a rapid and persistent therapeutic response is needed, but at the same time, contraindications to anti-TNFα treatment, such as the concomitant TB infection in our patient, are present.

References

1 Emmi G, Silvestri E, Squatrito D, *et al.* Behçets syndrome pathophysiology and potential therapeutic targets. *Intern Emerg Med* 2014; 9: 257–265.
2 Emmi G, Silvestri E, Cameli AM, *et al.* Anakinra for resistant Behçet uveitis: why not? *Clin Exp Rheumatol* 2013; 31: 152–153.

3 Ugurlu S, Ucar D, Seyahi E, *et al.* Canakinumab in a patient with juvenile Behçets syndrome with refractory eye disease. *Ann Rheum Dis* 2012; **71**: 1589–1591.
4 Cantarini L, Vitale A, Borri M, *et al.* Successful use of canakinumab in a patient with resistant Behçets disease. *Clin Exp Rheumatol* 2012; **30**: 115.
5 Emmi G, Silvestri E, Ciucciarelli L, *et al.* Reply to: anti-IL1 blocking agents in drug-resistant Behçets syndrome: our little case series. *Clin Exp Rheumatol* 2014; **84**: 172.
6 Gül A, Tugal-Tutkun I, Dinarello CA, *et al.* Interleukin-1β-regulating antibody XOMA 052 (gevokizumab) in the treatment of acute exacerbations of resistant uveitis of Behçets disease: an open-label pilot study. *Ann Rheum Dis* 2012; **71**: 563–566.
7 Emmi G, Talarico R, Lopalco G, *et al.* Efficacy and safety profile of anti-interleukin-1 treatment in Behçets disease: a multicenter retrospective study. *Clin Rheumatol* 2015. (Epub ahead of print).
8 Cantarini L, Lopalco G, Caso F, *et al.* Effectiveness and tuberculosis-related safety profile of interleukin-1 blocking agents in the management of Behçets disease. *Autoimmun Rev* 2015; **14**: 1–9.
9 Cantarini L, Talarico R, Generali E, *et al.* Safety profile of biologic agents for Behçets disease in a multicenter observational cohort study. *Int J Rheum Dis* 2015;. doi:10.1111/1756-185X.12732.
10 Lopalco G, Cantarini L, Vitale A, *et al.* Interleukin-1 as a common denominator from autoinflammatory to autoimmune disorders: premises, perils, and perspectives. *Mediators Inflamm* 2015; **2015**: 194864.
11 Cantarini L, Lopalco G, Cattalini M, *et al.* Interleukin-1: Ariadnes thread in autoinflammatory and autoimmune disorders. *Isr Med Assoc J* 2015; **17**: 93–97.
12 Gül A. Behçets disease as an autoinflammatory disorder. *Curr Drug Targets Inflamm Allergy* 2005; **4**: 81–83.
13 Zou J, Guan JL. Interleukin-1-related genes polymorphisms in Turkish patients with Behçet disease: a meta-analysis. *Mod Rheumatol* 2014; **24**: 321–326.
14 Liang L, Tan X, Zhou Q, *et al.* IL-1β triggered by peptidoglycan and lipopolysaccharide through TLR2/4 and ROS-NLRP3 inflammasome-dependent pathways is involved in ocular Behçets disease. *Invest Ophthalmol Vis Sci* 2013; **54**: 402–414.

