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# Tocilizumab in severe and refractory Behcet's disease: Four cases and literature review

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ABSTRACT

*Introduction:* In Behcet's disease (BD), interleukin (IL)-6 drive the immune-mediated inflammatory process. The IL-6 receptor can be targeted using tocilizumab. As an off-label treatment, we tested its efficacy in patients with BD.
*Methods:* Overall, 4 patients with refractory BD were treated with tocilizumab, 8 mg/kg/4 weeks. Patients were clinically and biologically assessed before administering each dose and the literature was reviewed.
*Results:* Tocilizumab was found to be safe and well tolerated. BD activity decreased significantly in all patients, and prednisone dose was reduced in all cases (up to 50% of the baseline dose). Treatment appeared effective in alleviating skin/mucosal effects, neurological involvement, and uveitis, but less effective for arthralgia and abdominal pain. A very short time lag between the onset of treatment with tocilizumab and the clinical response was observed. The literature review revealed 11 previous cases reporting improvement to BD with this treatment, and 3 previous cases without efficacy.
*Conclusions:* We reported the most important study treating refractory BD with tocilizumab; this treatment could be safe and efficient, but will require further evaluation by randomized clinical trials.


## Introduction

Behcet's disease (BD) is a systemic inflammatory disease defined mainly by clinical symptoms [1] including recurrent aphthous and genital ulcers, skin, and joint effects as well as posterior uveitis. BD could be associated with digestive, neurological, and cardiovascular symptoms. The therapeutic arsenal is mainly composed of classical immunosuppressors and immunomodulators (azathioprine, cyclosporine A, and interferon alpha), and more recently anti-TNF alpha agents [2]. However, when faced with resistance to these treatments, no alternative therapeutic strategy is currently recommended.

Several studies have shown levels of circulating interleukin (IL)-6 to be elevated in patients with BD [3]; T lymphocytes and monocytes from these patients produce significantly higher levels of IL-6 than cells from healthy donors *in vitro* [4]. Studies on cerebrospinal fluid (CSF) showed that IL-6 is the only cytokine to be increased in BD when neurological effects are present [5]. Finally, the circulating IL-6 levels correlate with the activity of the disease [6,7]. IL-6 could therefore be a relevant therapeutic target for refractory BD and its activity can be blocked using tocilizumab. *In vitro*, blocking IL-6 affects the TH17/Treg ratio by reducing the capacity of naive T lymphocytes to differentiate into Th17 lymphocytes [8]. This has been confirmed in murine models [9].

In this article, we reported the results of 4 patients with refractory BD treated with tocilizumab, a monoclonal anti-IL-6-receptor antibody. It was the most important cases series using this treatment for BD; then we synthesized the previous published data of 10 cases.

## Materials and methods

Overall, 4 patients with BD, as defined by the diagnostic criteria [1], were treated with tocilizumab. All patients had a serious disease, which had failed to respond to several therapies. The dose used was 8 mg/kg every 4 weeks. Before each monthly dose, patients were clinically and biologically assessed using the "Behcet's disease current activity form" (BDCAF) [10]. Concomitant treatments, any side effects, and the dose of steroids (expressed as a prednisone equivalent) were recorded.

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Response and remission of intraocular inflammation were assessed using the uveitis nomenclature described by the Standardization of Uveitis Nomenclature (SUN) Working Group [11]. Response was defined as a two-step decrease in level inflammation, or decrease to grade 0 from their initial values, and remission was defined as scores becoming 0 for 3 months or more.

A literature review was also conducted to gather all cases of patients with refractory BD who had been treated with tocilizumab. A search was performed in PubMed using the terms "*tocilizumab*" and "*Behcet disease*," and only articles in English were retained.

Statistical analysis was performed using non-parametric test (Mann and Whitney) to compare continuous variables.

## Results

### *Cohort of 4 patients*

Overall, 4 patients with BD were treated with tocilizumab. The 4 patients were all carriers of the HLA B51 allele. Their disease was refractory to the currently recommended treatments (Fig. 1), i.e., corticotherapy (4 patients), common immunosuppressors including azathioprine, methotrexate, and/or cyclosporine ($n = 4$), interferon alpha ($n = 1$), adalimumab ($n = 4$), infliximab ($n = 3$), golimumab ($n = 2$), and anakinra ($n = 1$).

### *Case 1*

The first patient was a 23-year-old woman with refractory BD and eye involvement (relapsing posterior uveitis; Fig. 2), aphthous and genital ulcers (one recurrence per months), skin (cutaneous hypersensibility), joint (bilateral polyarthralgias involving ankle, wrist, elbow, shoulder with recurrent gonarthritis), and digestive symptoms (abdominal pain and 3 episodes of diarrhoeas per weeks) since she was 16-year old. Diagnosis was made according to disease criteria, and all others diagnosis were ruled out (coloscopy, colic biopsy, immunology, etc.). She had a past treatment story of immunosupressor for 2 years (azathioprine and cyclosporine); interferon was inefficient; infliximab (5 mg/kg/4 weeks) was efficient for 2 years, adalimumab (40 mg/week) for 1 year then uveitis relapsed; anakinra (100 mg/d) was inefficient for joint, ocular, and digestive symptoms. At the time of introducing treatment with tocilizumab, 6 months after anakinra was discontinued, she was strongly corticodependent, receiving 30 mg/d, the activity score for her disease was 7/12, and it had a major impact on quality of life (Health Assessment Questionnaire or HAQ score: 0.625). Bilateral visual acuity was limited to 20/200, inflammatory grading of anterior chamber was 0.5+, 1+ for left vitreous haze, and fluorescein angiography showed, vascular leakage from retinal vein, retinal leakage at the posterior pole and macular edema. After 6 months' treatment (6 infusions), the relapsing uveitis disappeared with no anterior or vitreous inflammation (Fig. 2), the bilateral visual acuity improved to 20/40, the aphthous ulcers and genital sores had improved (only 1 recurrence upon 6 months), but the pain in the digestive tract and polyarthralgia persisted. After 12 months, ocular and mucosal remission remained; the activity score was reduced to 2/12 and corticotherapy was administered at 10 mg/d without relapse. The HAQ score had improved to 0.375. No side effect was noted in this patient; after 12 months, tocilizumab treatment was disconti-

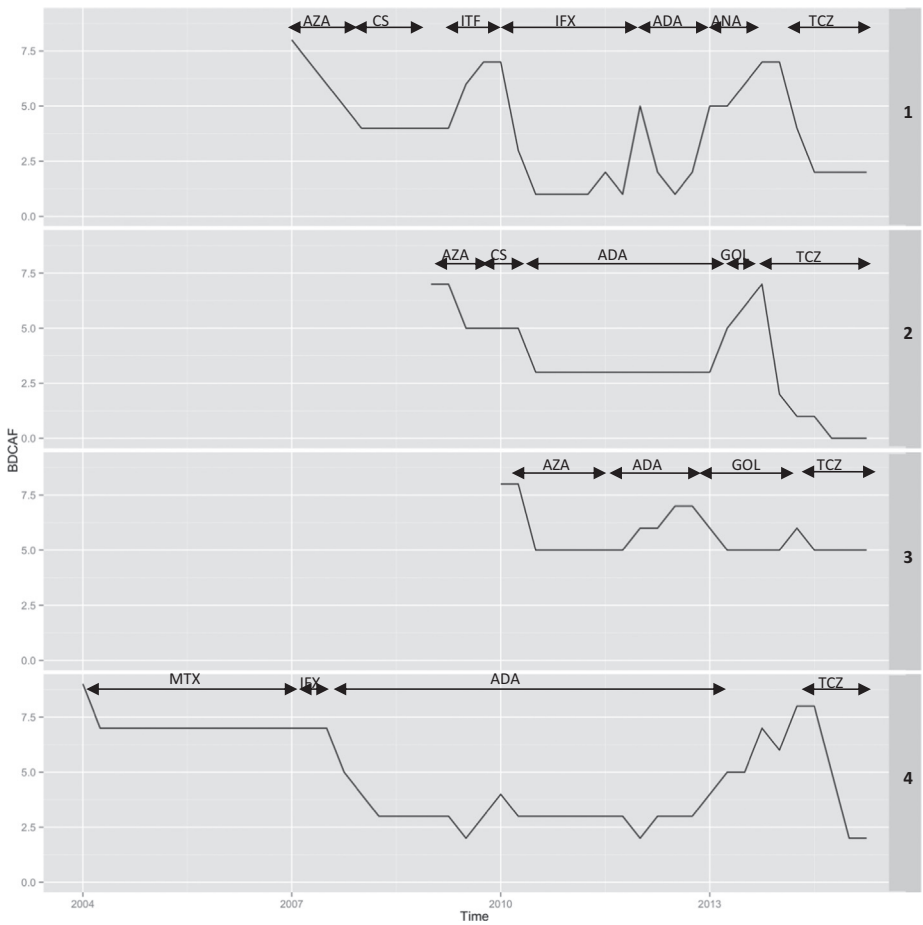


**Fig. 1.** Various treatment courses and responses for each patient (cases 1, 2, 3, and 4). Therapeutics responses were reported using BDCAF scoring [10] evaluated each 3 months. AZA, azathioprine; CS, cyclosporine; MTX, methotrexate; ITF, interferon alpha; IFX, infliximab; ADA, adalimumab; TCZ, tocilizumab; GOL, golimumab.