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## CASE REPORT

# Successful Treatment of Refractory Behçet's Disease with the TNF- $\alpha$ Blocker Infliximab

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## INTRODUCTION

Behçet's disease (BD) is an autoimmune, chronically relapsing, multisystemic, inflammatory disorder, classified among the vasculitides (1). So far, the pathogenesis of BD is not completely understood but most of the symptoms of the disease are attributed to small-vessel vasculitis. BD is prevalent in the Middle East, Asia, Japan and is rare among Caucasians. The disease affects more men than women and tends to develop mainly in the third to fourth decade of life (2). As there are no pathognomonic laboratory parameters, the diagnosis is suspected by the simultaneous or sequenced appearance of certain symptoms. According to the International Study Group criteria for BD, these include the presence of oral aphthae (at least three times in one year) plus any of two of the following symptoms: recurrent genital aphthae, ocular lesions (uveitis), skin lesions (erythema nodosum, pseudofolliculitis), positive pathergy test and/or organ involvement (lung, joints, brain and/or gastrointestinal tract). The frequencies of these symptoms were published by the "Behçet's syndrome research committee of Japan" and are summarized in Table 1. A number of heritable risk factors for BD have been reported (1). These include among others HLA-haplotypes B51 (positive in more than 60% of patients), 12 and 27; polymorphisms in gene loci encoding certain complement proteins, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), members of the heat shock protein family (HSP) as well as the MHC class I chain-related proteins (MIC); factor V Leiden mutation resulting in venous occlusion; intercellular adhesion molecule (ICAM) polymorphisms and, abnormalities in killing inhibitory receptors (KIR) (3).

**Keywords: Behçet's Disease, Infliximab, TNF-alpha, Hepatitis B**

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Although there is no cure for BD, the patients usually can control their symptoms with symptomatic medications, rest and/or exercise. The goal of treatment is to reduce discomfort and to prevent serious complications such as disability from arthritis or blindness. Usually, a combination of therapeutic regimens is necessary. Conventional therapies include high dose oral corticosteroids with/without other immunosuppressive agents such as azathioprine, cyclosporine, cyclophosphamide, colchicine, interferon- $\alpha$  or thalidomide (4). Unfortunately, some BD patients do not respond sufficiently to these therapies or the therapy is accompanied by considerable side effects.

It has been demonstrated recently that sera of BD patients contain significantly higher amounts of TNF- $\alpha$  than those of control individuals (5). It is also known that the immune response in BD patients is shifted toward the Th1 (cellular immunity) arm, presumably because of polymorphisms in the IL-12 promoter region and the TNF- $\alpha$  genes leading to an increased accumulation of TNF- $\alpha$  in the serum (6). Additionally, Ohno S. et al. and Tugal-Tutkun I. et al. have recently documented that TNF- $\alpha$  blocker infliximab can be of beneficial use in BD patients (7,8).

Because all these observations speak in favor of the pathogenic role of TNF- $\alpha$  in BD, we decided to use infliximab (Remicade<sup>®</sup>) in two patients with predominantly ocular BD who had failed to respond successfully to conventional systemic therapies.

**Table 1. Behçet's disease: diagnostic criteria**

Major		Minor	
	%		%
Oral ulceration - recurrent'	97-98	Arthritis and arthralgia'	45-50
Genital ulceration	80-90	Neurological lesions'	5-25
Ocular Inflammation'	50	Vasculitis'	25
Skin lesions	80	Gastrointestinal lesions'	0-25
erythema nodosum, folliculitis/acne'		Cardiovascular lesions'	
Pathergy test		Epididymitis'	8

The diagnostic criteria of Behçet's disease are based on major and minor clinical symptoms. The diagnosis is considered: a) complete when four major features, b) incomplete when (i) 3 major features, (ii) 2 major and 2 minor features, or (iii) typical ocular symptom and 1 major or 2 minor features and c) possible when (i) 2 major features or (ii) 1 major and 2 minor features, are present. HLA-B5 [and its subclass (split antigen) 51 allele], 12 and 27 status have been related to Behçet's disease.

## CASE REPORT

Patient number 1, a 56 year-old man of Turkish ethnicity presented himself with oral aphthae, bilateral uveitis, arthralgia and cerebral vasculitis. The patient also suffered from a chronically active hepatitis B virus (HBV) infection (positive HBsAg, HBeAg, HBcAb parameters and HBV viral load of 362000 IU/ml). The HLA-B51, B12 and B27 haplotypes were negative in this patient. His BD was irresponsive to previous treatment regimens such as high-dose prednisone, cyclophosphamide, thalidomide, chlorambucil, colchicine, hydroxychloroquin, azathioprine and high dose intravenous immunoglobulins (IVIG). Alternative therapies such as interferon- $\alpha$  or pegylated interferon were not considered because of the patient's low compliance and his severe preexisting depression (9).

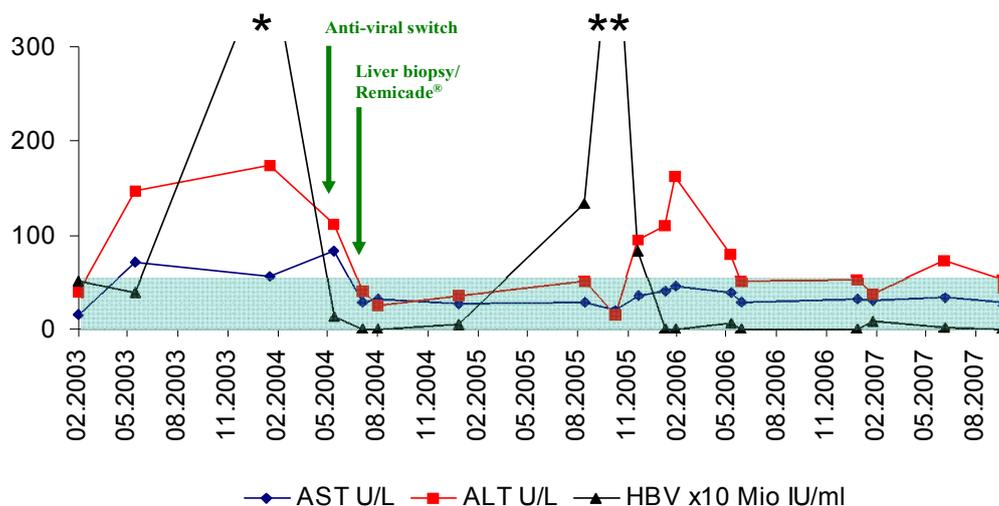
Patient number 2 was a 35 year old man also of Turkish ethnicity suffering from oral aphthae, bilateral uveitis, and arthralgia. He had the HLA-B51<sup>+</sup>/B12<sup>+</sup> haplotype. The unsatisfying previous treatment regimens comprised high-dose prednisone, thalidomide and methotrexate.

In both of these patients, active/latent tuberculosis was excluded using a chest X-ray, a Mendel Mantoux Test (MMT) as well as a newly developed tuberculosis-specific quantiFERON<sup>®</sup>-Tb test (Cellestis Inc., Darmstadt, Germany) (10).

Infliximab (Remicade<sup>®</sup>, Centocor BV, Netherlands) was administered according to published guidelines at the dose of 5 mg/kg body weight at week 0, 2, 6 and then every 8 weeks (11). Regular gastroenterological, ophthalmologic and neurological controls and, when indicated, magnetic resonance imaging (MRI) of the brain was performed to exclude cerebral vasculitis.

So far, the therapy has been tolerated without any complications (follow up > 54 and 31 months, respectively) and the patients are free of clinical manifestations of the disease.

In the case of patient 1, the chronically active hepatitis B infection required a gastroenterological consultation and a liver biopsy was performed prior to therapy. The biopsy showed slight portal and lobular inflammation activity, slight fibrosis (stage II according to Batts and Ludwig classification), no steatosis and Metavir score of A1 and F2 (12,13). A liver ultrasound performed at this time was also normal. The patient's HBV infection had been previously treated with lamivudine (Epivir<sup>®</sup>) until three months prior to Remicade<sup>®</sup> start when he developed virus resistance to lamivudine [as demonstrated by sudden increase in liver function parameters (LFP), HBV viral load, and diagnosed by viral mutation analysis using polymerase chain reaction technique (PCR), (Figure 1)]. At this time the HBV-specific therapy was successfully switched to 245 mg oral tenofovir daily (Viread<sup>®</sup>, Gilead Sciences Inc. Martinsried/Munich, Germany) (14). We continuously monitored the liver function parameters (LFP) namely AST, ALT and  $\gamma$ GT (every month), and the HBV viral load (every three months). After starting with Remicade<sup>®</sup>, peaking of LFPs was observed once (Figure 1). This was due to the patient's low compliance resulting in a self discontinuation of the HBV therapy. The values got into normal range after re-establishment of the therapy with tenofovir (Viread<sup>®</sup>) (Figure 1). So far, chronic HBV infection has been well controlled without any additional interventions.



**Figure 1.** Exacerbation of the LFP and viral load of the patient 1 were observed twice. The first peak [\* , before infliximab (Remicade<sup>®</sup>) start] was associated with viral resistance [diagnosed by hepatitis virus polymerase chain reaction (PCR) analysis] to lamivudine (Epivir<sup>®</sup>) [therapy switched to tenofovir (Viraed<sup>®</sup>)] and the second one (\*\*) with low compliance. Apart from that LFPs were in normal range (green shadow) (Mio IU/ml: million international units/ml).The colourful version is available at: [www.iji.ir](http://www.iji.ir)

## DISCUSSION

Behçet's disease is a chronically relapsing disease caused by the inflammatory damage of blood vessels with no invariably effective treatment. We present two patients suffering from BD with uveitis as their major complaint. They were refractory to conventional therapies, but responded successfully to the TNF- $\alpha$  blocker infliximab. Clinical response started after administration of the second cycle of infliximab.

The first patient was a 56 year old man with oral aphthae, uveitis, arthralgia, CNS-involvement and a chronically active HBV infection. The second patient, a 35 year old man, suffered from oral aphthae, uveitis and arthralgia. After having excluded latent tuberculosis, both patients received infliximab, so far without any complications (follow up > 54 and 31 months, respectively). The chronically active HBV infection in the first patient was under control with simultaneous administration of tenofovir. The liver function parameters (LFPs) and HBV viral load remained constant during the entire observation period.

We speculate that blocking of TNF- $\alpha$  by infliximab (Remicade<sup>®</sup>) in BD patients should shift the Th1-deviated immune response in these patients toward the Th2 arm and therefore lead to the clinical response (6).

This study shows that: a) infliximab can be an effective treatment for ocular BD especially in patients refractory to conventional therapies and, b) concomitant HBV infection is not a contraindication for treatment with infliximab in BD when the LFPs are in normal range.

## ACKNOWLEDGEMENT

No conflict of interest declared.

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