

Infliximab for the Treatment of Neuro-Behçet's Disease: A Case Series and Review of the Literature

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Introduction

Behçet's disease (BD) is a vasculitis in which the hallmark lesions are oral and often genital ulcers. Involvement of parenchymal central nervous system (neuro-Behçet's) is a serious complication commonly characterized by brainstem and/or basal ganglia lesions. To date, treatment of neuro-Behçet's remains largely empirical, and may not adequately control the disease (1).

Serum tumor necrosis factor α (TNF α) levels are increased in active BD (2), suggesting a role for TNF α in disease pathogenesis. Clinically, significant improvement of various BD manifestations has been reported with TNF α blockade (3). However, evidence for the efficacy of TNF α blockers in the treatment of neuro-Behçet's is scant. We present 8 patients with neuro-Behçet's who responded favorably to infliximab therapy and review the relevant literature.

Case Series

Case 1. A female patient born in 1958 was diagnosed in 1999 with BD according to the International Study Group for Behçet's Disease criteria (ISGC; bipolar aphthosis, erythema nodosum, pseudofolliculitis, and papulopustular lesions) (4); she also had arthritis. In 2004, the patient developed fever, diplopia, VIII left nerve deficiency, and paresthesia affecting the right face and arm. Magnetic resonance imaging (MRI; December 2004) showed ischemic lesions in the pons, pons-mesencephalon junction, and

white matter in the right internal capsula. The patient was treated with pulse cyclophosphamide and high-dose glucocorticoids (GC) with a tapering scheme with clinical benefit, but the diplopia and the right-sided paresthesia recurred when the prednisone dosage was tapered to 1.25 mg/day. The patient was referred to us. Investigations including purified protein derivative, HLA-B51, and chest radiograph were normal or negative. MRI showed the lesions previously described and a new nonenhancing lesion in the pons near the left IV ventricle floor consistent with vasculitis (Figure 1). The patient was treated with prednisone 50 mg/day, methotrexate 20 mg/week with folic acid, and infliximab 5 mg/kg at weeks 0, 2, and 6 and bimonthly thereafter. The neurologic manifestations remitted quickly, and a repeat MRI (January 2006) demonstrated resolution of the lesion near the IV ventricle floor (Figure 2).

Case 2. In 2005, a male patient born in 1969 developed fever, erythema nodosum, pustulosis, and pseudofolliculitis on the background of major oral aphthosis. In November 2005, he presented with headache, diplopia, dysarthria, anisocoria, and left-sided neurologic deficit, and in December he had a rectal hemorrhage. Tests for pathogens including *Treponema*, *Borrelia*, and *Mycobacterium tuberculosis*; tumor markers; autoimmune serology including antiphospholipid antibodies and lupus anticoagulants; and echocardiography were normal or negative. Cerebrospinal fluid (CSF) analysis demonstrated increased protein (90 mg/dl) and lymphocytes (80 cells/mm³) but no oligoclonal bands. Visual evoked potentials and electromyography were unremarkable. MRI showed multiple high-signal lesions in T2-weighted sequences involving the subthalamus, mesencephalon, optic tract, and dorsal pons on the right side spreading to the thalamus and internal capsule. Empirical treatment (antibiotics, antiviral agents, and GC) was ineffective. A stereotactic brain biopsy revealed predominantly perivascular macrophages, CD3+ T cells (CD4:CD8 ratio 1:1), and rare CD20+ B cells and polymorphonuclear cells with scattered intraparenchymal foci and sparse areas of demyelination. The patient was

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Figure 1. Axial fluid-attenuated inversion recovery image (repetition time 11,000 msec; echo time 2,800 msec). High-signal intensity in the dorsal pons, near the IV ventricle (arrows) is seen. Note the presence of mass effect.

referred to us. Laboratory tests were noncontributive except for positive HLA-B51. MRI (February 2006) demonstrated high-signal lesions in the right substantia nigra and cerebral peduncle with mild enhancement in the middle of the mesencephalon but an intact spinal cord. Neuro-Behçet's was diagnosed and prednisone 50 mg/day with infliximab (5 mg/kg at weeks 0, 2, and 6 and bimonthly thereafter) was started. The patient's clinical lesions gradually resolved. MRI showed marked improvement of the lesions involving the right substantia nigra and cerebral peduncle in June 2006 and almost complete resolution of the lesions in the right substantia nigra and cerebral peduncle in October. Currently (January 2007) the patient remains in full remission, and GC treatment is gradually being tapered.

Case 3. A female patient born in 1970 who was diagnosed at age 18 with BD according to the ISGC (erythema nodosum, arthritis, bipolar aphthosis, and papulopustular lesions with positive HLA-B51) presented in 2000 with hemiparesis of the right face, arm, and leg followed by partial seizures in 2001. Treatment with cyclosporine 3 mg/kg/day, methylprednisolone 16 mg/day, methotrexate 20 mg/week, and antiepileptic medications was ineffective and the patient developed generalized seizures. Therefore, cyclosporine was withdrawn and infliximab (5 mg/kg at weeks 0, 2, and 6 and every 6–8 weeks thereafter) was started. No brain MRI was performed prior to starting infliximab therapy. The clinical manifestations improved gradually over the following months and the GC dose was

tapered. MRI 6 months later showed only a small nonenhancing parenchymal lesion in the right frontoparietal area at the cortico-subcortical junction (hypointense in T1 and mildly hyperintense in T2; fluid-attenuated inversion recovery [FLAIR] sequences) consistent with vasculitis-induced damage. In June 2006, infliximab was withdrawn because of gradual loss of efficacy, but after suspension the neurologic manifestations flared. However, the patient improved again while receiving methotrexate 20 mg/week and etanercept 50 mg/week, with only occasional headaches and a single episode of absence seizures.

Case 4. A male patient born in 1984 was diagnosed at age 13 with BD according to the ISGC (bipolar aphthosis and papulopustular lesions). Medical history revealed otherwise recurrent fever, headache, and hypertension. HLA-B51 was negative. In June 2000 the patient developed sudden-onset left posterior uveitis and left-sided hemiparesis. MRI apparently showed evidence of white matter lesions (full report not available to us). The patient was treated with GC and azathioprine (150 mg/day), but his disease remained active with persistence of pseudofolliculitis, left-sided hemiparesis, and cerebellar signs. A repeat MRI disclosed focal lesions in the pons, right mesencephalon, right internal capsule, and in the putamen and thalamus posteriorly on the right side. Ophthalmologic examination demonstrated bilateral papillitis and retinal vasculitis. Treatment with pulse cyclophosphamide and prednisone 25 mg/day was started, followed first by therapy with oral cyclophosphamide (150 mg/day) for ~2 years and prednisone (mean dosage 15 mg/day), and sub-



Figure 2. Axial fluid-attenuated inversion recovery image (repetition time 11,000 msec; echo time 2,800 msec). Six-month follow-up shows complete regression of the lesion involving the left pons.

sequently (June 2004) azathioprine 150 mg/day. MRI (June 2004) showed more widespread lesions with nonenhancing focal lesions in the right pons and right thalamus and white matter laterally and superiorly to the ventricles bilaterally. Because of active neurologic and ocular features, in November 2004 azathioprine was withdrawn and infliximab (5 mg/kg at weeks 0, 2, and 6 and bimonthly thereafter) was started. MRI (February 2005) was basically unchanged, but the ocular disease remitted and the neurologic manifestations improved.

Case 5. A male patient born in 1964 had clinical manifestations since 1999 that were suggestive of BD (erythema nodosum, papulopustular lesions, epididymitis, and fever). Medical history revealed otherwise bilateral hearing loss. In April 2006, the patient developed sudden-onset left-sided face hemiparesis, vertigo, and visual loss in the left eye diagnosed as anterior ischemic optic neuritis. Antineutrophil cytoplasmic antibodies (ANCA) were positive at a low titer. ANCA-associated vasculitis was diagnosed and therapy with prednisone 50 mg/day with cyclosporine 3 mg/kg/day was started. However, in August 2006, his left-sided face hemiparesis recurred, while his mental status deteriorated rapidly. The patient was referred to us. On admission, the patient was lethargic, dysphasic, and unable to stand unaided; the skin showed widespread papulopustular lesions. HLA-B51 and pathergy test were positive, whereas ANCA tested negative. MRI disclosed high-signal small lesions in T2 and FLAIR sequences in the right central part of the mesencephalon (enhancing) and in the right internal capsule (nonenhancing). We diagnosed neuro-Behçet's and administered infliximab 5 mg/kg at weeks 0, 1, 3, and 8 and bimonthly thereafter with substantial amelioration of the patient's mental status and gait. A repeat MRI (November 2006) demonstrated a reduction in the abnormal signal in the mesencephalon, while a subsequent scan (December 2006) showed no evidence of active lesions. The patient is currently doing well with infliximab treatment associated with prednisone 25 mg/day with minor neurologic sequelae.

Case 6. A male patient born in 1933 was diagnosed in 1996 with BD based on recurrent oral ulcerations, papulopustular lesions, and left uveitis. His clinical background included hepatitis B and C infection (active hepatitis was excluded by persistently normal liver enzymes) and hypertension. He was initially treated with GC and cyclosporine (3 mg/kg/day) with clinical benefit except for his ocular disease, which progressed to partial unilateral visual loss. However, in 2002, while receiving cyclosporine (2 mg/kg/day), the patient developed fever, an altered mental status, and loss of consciousness. He was admitted to his local hospital.

Physical examination revealed partial visual loss of the left eye and weak tendon jerks. CSF analysis showed increased protein but negative tests for bacteria and fungi. MRI demonstrated high-signal lesions in long-relaxation time sequences located in the left temporal region and hippocampus, in the right frontal region near the ventricle,

in the caput of the left nucleus caudatus, and subcortically bilaterally with involvement of the nucleus lenticularis. The lesions in the hippocampus and in the nucleus caudatus were enhancing. Neuro-Behçet's was diagnosed. Cyclosporine was withdrawn and treatment with 3 methylprednisolone pulses followed by infliximab 5 mg/kg at weeks 0, 2, and 6 was started with resolution of the neurologic manifestations. A repeat MRI (January 2003) showed a significant improvement in the lesions observed previously, while a further scan in August 2006 demonstrated only small, nonenhancing high-signal areas in T2-weighted sequences in the left temporal region. The patient has subsequently remained in remission apart from sporadic papulopustular lesions while receiving chlorambucil 5 mg/day (withdrawn at the end of August 2006) and low-dose GC.

Case 7. A male patient born in 1962 was diagnosed with BD in 1999 (bipolar aphthosis and erythema nodosum). He was positive for HLA-B51. The patient subsequently developed recurrent bilateral uveitis, papulopustular lesions, and joint pain. Treatment with colchicine was not effective, whereas cyclosporine (3 mg/kg/day throughout 2000) and methylprednisolone pulse therapy as required were effective in treating his uveitis. After attaining disease remission, the patient was treated with low-dose prednisone. In 2003, he developed severe headache, right-sided hemiparesis, slurred speech, and memory loss. MRI (February 2003) showed a nonenhancing high-signal lesion in T2-weighted and FLAIR sequences involving the anterior median part of the pons and mesencephalon on the left side. Neuro-Behçet's was diagnosed and infliximab 5 mg/kg was administered with a good clinical response across the board, while GC could be gradually tapered. A repeat MRI (June 2006) documented only a small (low signal in T1-weighted sequences and high signal in T2-weighted sequences) area in the pons anteriorly judged to be ischemic.

Case 8. A male patient born in 1971 was diagnosed in 1990 with BD according to the ISGC (bipolar aphthosis and papulopustular lesions). In 1995, he experienced recurrent arthritis that responded to cyclosporine 3 mg/kg/day and colchicine 1 mg/day. In June 2006, the patient reported headache and dizziness of 2 weeks' duration, and in November 2006 he had an episode of diplopia. MRI showed high-signal lesions in T2-weighted and FLAIR sequences in the right posterior pons with involvement of the ipsilateral cerebellar peduncle and bulbar lesions; diffuse meningeal enhancement was also observed. Neuro-Behçet's was diagnosed and treatment with infliximab 5 mg/kg at weeks 0, 2, and 6 and every 8 weeks thereafter was started. The diplopia resolved within 5 days, and MRI performed in January 2007 was unremarkable.

Discussion

Four articles (PubMed search up to January 2007) on anti-TNF α therapy for Neuro-Behçet's have been published (each reporting a single patient) (5–8). In the present report, we present 8 additional patients.

Table 1. Cases of neuro-Behçet's treated with infliximab in the present study*								
Patient	ISG	IFX dose	Indication for IFX	Previous therapy	Adjunct therapy	Outcome	Followup	Receiving IFX at followup
1	Yes	5 mg/kg	Relapse of neuro-Behçet's	PD 1.25 mg/day	PD 50 mg/day, MTX 20 mg/week	Clinical improvement and reduction in MRI lesions	In remission on IFX 5 mg/kg every 2 months	Yes
2	No	5 mg/kg	New-onset neuro-Behçet's	PD, unspecified dose	PD 50 mg/day	Clinical improvement and reduction in MRI lesions	In remission on IFX 5 mg/kg every 2 months	Yes
3	Yes	5 mg/kg	New-onset neuro-Behçet's	Cyclosporine 3 mg/kg/day, MP 16 mg/day, MTX 20 mg/week	MTX 20 mg/week	Clinical improvement (no MRI available)	Gradual loss of IFX efficacy	No (switched to etanercept)
4	Yes	5 mg/kg	Relapse of neuro-Behçet's	AZA 150 mg/day, pulse CYC (1–1.5 gm), then oral CYC (150 mg/day); PD 15 mg day	PD 25 mg/day with a tapering scheme	Clinical improvement (no MRI available)	In remission	Yes
5	No	5 mg/kg	Relapse of neuro-Behçet's	CYC 50 mg/day; cyclosporine 3 mg/kg/day; PD 50 mg/day tapering to 10	PD 25 mg/day	Clinical improvement, no evidence of active lesions on MRI	Neurologic sequelae, otherwise in remission on IFX 5 mg/kg every 2 months	Yes
6	Yes	5 mg/kg	New-onset neuro-Behçet's	Cyclosporine 2 mg/kg/day	MP 1 gm 3 pulses	Clinical and MRI improvement	In remission on MP 4 mg day	No
7	Yes	5 mg/kg	New-onset neuro-Behçet's	Cyclosporine 3 mg/kg/day; colchicine 1 mg/day; MP pulses (1 gm each), PD 5 mg/day	PD 5 mg/day with a tapering scheme	Clinical and MRI improvement	In remission on IFX 5 mg/kg every 2 months	Yes
8	Yes	5 mg/kg	New-onset neuro-Behçet's	Cyclosporine 3 mg/kg/day, colchicine 1 mg/day	Cyclosporine 2.5 mg/kg/day, PD 25 mg with a tapering scheme	Clinical remission, resolution of MRI lesions	In remission on IFX 5 mg/kg every 2 months	Yes

* ISG = International Study Group criteria for Behçet's disease (4); IFX = infliximab; PD = prednisone; MTX = methotrexate; MRI = magnetic resonance imaging; MP = methylprednisolone; AZA = azathioprine; CYC = cyclophosphamide.

Table 2. Published cases of neuro-Behçet's treated with infliximab*

Ref.	ISG	IFX dose	Indication for IFX	Previous therapy	Adjunct therapy	Outcome	Followup	Receiving IFX at followup
5	No	5 mg/kg	Relapse of neuro-Behçet's	Not mentioned	CYC 1 gm/m ² given twice, pulse MP (1 gm/day for 3 days) given twice, then PD 50 mg/day	Resolution of clinical manifestations and MRI lesions	In remission at 1 month	No
6	Yes	5 mg/kg	New-onset neuro-Behçet's	GC, colchicine, cyclosporine, thalidomide	Pulse MP and pulse CYC, colchicine	Clinical improvement and reduction in MRI lesions (relapse after IFX withdrawal after 5 CYC pulses on PD 20 mg/day, response after reintroduction of IFX)	In remission 16 months after the relapse on IFX 5 mg/kg every 2 months, colchicine, and PD 10 mg/day	Yes
7	No	3 mg/kg	New-onset neuro-Behçet's	None	PD 60 mg/day	Resolution of clinical manifestations and MRI lesions	In remission at 12 months on PD 10 mg/day	No
8	Yes	3 mg/kg	New-onset neuro-Behçet's	Intravenous CYC, pulse MP, oral MTX	PD 60 mg/day tapered to 15	Clinical improvement, reduction in MRI lesions	In remission on PD 15 mg daily	No

* GC = glucocorticoids; see Table 1 for additional definitions.

None of our patients had a positive family history for BD. Six of 8 patients described by us and 2 of 4 patients reported in the literature met the ISGC for BD (Tables 1 and 2). In those who did not meet the ISGC, alternative diagnoses such as sarcoidosis, tuberculosis, autoimmune diseases, or other vasculitis could reasonably be excluded by the appropriate laboratory investigations and by the absence of typical clinical features. However, one of the patients reported in the literature (6) took illicit drugs known to cause cerebral parenchymal alterations, while in another reported patient the pattern of cerebral involvement was somehow unusual for neuro-Behçet's (5).

Infliximab was prescribed for new-onset neuro-Behçet's in 8 patients and for relapsing neuro-Behçet's in 4 patients with variable adjunct therapy (Tables 1 and 2). Administration regimens were broadly similar. All patients had a satisfactory clinical response to infliximab, while brain MRI showed at least partial regression of parenchymal lesions in all 10 patients who underwent MRI before and after infliximab treatment. At followup, virtually all patients were in remission. Six of our patients are still receiving infliximab, while 1 patient was switched to etanercept because of loss of efficacy of infliximab. In 1 patient, infliximab was safely withdrawn.

With regard to the published cases, 1 patient relapsed upon infliximab withdrawal, but remitted again after infliximab was reintroduced (6), whereas in 3 other patients, infliximab was safely withdrawn. Taken together, these data suggest that infliximab may be effective in treating neuro-Behçet's. In one case, the clinical benefit conferred by infliximab was paralleled by decreased CSF levels of the inflammatory cytokines TNF α , interleukin-1 β (IL-1 β), and IL-6 (8).

Our study has some limitations. First, the study was retrospective, therefore the assessment of patients was not fully standardized, although all patients were reviewed by a neurologist and most of them underwent brain imaging studies. Second, the documentation of patients referred to us was not always fully available. Third, because infliximab was administered after as well as with other medications, the clinical benefit observed may reflect, at least in part, the effect of other drugs. However, because some patients (e.g., patients 2, 3, 4, 5, and 7 in our study, and the patient in reference 8) were receiving drugs to which they had previously failed to respond, we believe that their favorable clinical response is likely to be due to infliximab, because such response was fairly rapid, as reported for other manifestations of patients with BD treated with infliximab (3). Conversely, in patients 3 and 6 cyclosporine treatment was ongoing after the onset of neurologic manifestations and was withdrawn shortly before infliximab

therapy. Because cyclosporine has been implicated in inducing or worsening neurologic features in BD (1), we cannot exclude that withdrawal of this drug at onset of infliximab therapy may have contributed to the favorable response observed in these patients. We cannot adequately comment on the long-term efficacy of infliximab as maintenance therapy for neuro-Behçet's because followup duration was fairly limited in many patients and infliximab was discontinued in a few patients. In the sample reported herein, neuro-Behçet's flared in only 1 of the 4 patients in whom infliximab was discontinued (6). No infliximab-related serious adverse events occurred. Infliximab appears to be a promising agent for remission induction and possibly for maintenance therapy of neuro-Behçet's.

AUTHOR CONTRIBUTIONS

Dr. Salvarani had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Salvarani.

Acquisition of data. Pipitone, Olivieri, Padula, D'Angelo, Nigro, Zuccoli, Boiardi.

Analysis and interpretation of data. Olivieri, Padula, D'Angelo, Nigro, Zuccoli, Boiardi, Salvarani.

Manuscript preparation. Pipitone, Zuccoli, Salvarani.

Statistical analysis. Boiardi.

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