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CASE BASED REVIEW

Infliximab for patients with neuro-Behcet's disease: case series and literature review

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Abstract This study aims to report the therapeutic effects of anti-tumor necrotic factor antibody, infliximab, for treatment of neuro-Behcet's disease (NBD) and to review the literature. We described four patients (all male, median age 40 years old) who fulfilled the International Study Group criteria for Behcet's disease (BD) and presented with neurological complication. Demographic and clinical characteristics of the patients, dose, therapeutic effects, and adverse drug reaction (ADR) of infliximab were reported. Two patients had secondary progressive, one relapsing progressive, and one primary progressive course (median duration of BD and NBD 11 and 2 years, respectively). Two patients each received infliximab with 3 and 5 mg/kg infusions, respectively. The patients received infliximab for median of 22 weeks. Clinical responses were unsatisfactory for two patients on 3 mg/kg regimen; and good in two patients on 5 mg/kg and monthly intravenous 500–1,000 mg cyclophosphamide. Varicella zoster infection was seen as a major ADR in one patient. Our results with infliximab were not as promising as the previous reports. Infliximab, 5 mg/kg per dose with adjuvant immunosuppressive therapy, is probably more effective than other regimens.

Keywords Anti-tumor necrotic factor antibody · Behcet syndrome · Behcet's disease · Infliximab · Neuro-Behcet's disease

Dedication In memory of our deceased patients.

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Abbreviations

TNF	Tumor necrotic factor
CSF	Cerebrospinal fluid
INFX	Infliximab
COL	Colchicines
Cs	Corticosteroids
AZT	Azathioprine
CTX	Cyclophosphamide
CsA	Cyclosporine A
PDSN	Prednisolone
MTX	Methotrexate
IVMP	Intravenous methylprednisolone

Introduction

Neuro-Behçet's disease (NBD) is the constellation of particular neurologic syndromes as a direct result of Behcet's disease (BD). Central nervous system involvement in NBD is categorized into two main subdivisions:

parenchymal NBD including brainstem, hemispheral, spinal, meningoencephalitic or mixed involvements; and non-parenchymal NBD including dural sinus thrombosis, pseudotumor cerebri, arterial occlusion, and/or aneurisms. A less common mixed parenchymal and non-parenchymal subgroup can be considered in some patients [1, 2].

There are plenty of controversies in treatment of NBD [3]. Corticosteroids (Cs) and disease-modifying anti-rheumatic drugs have been used conventionally but "biologics" have been advocated recently. As tumor necrosis factor (TNF)-alpha is believed to have a crucial role in etiology of BD, TNF-alpha blockade has been advocated for treatment of different manifestations of BD [4].

Here, we report our experience in administration of anti-TNF antibody, infliximab (INFX), for treatment of NBD and review the literature.

Case reports

All patients fulfilled the International Study Group criteria for BD [5] and referred to BD clinic affiliated to Shiraz University of Medical Sciences, Shiraz, southern Iran, from January 2006 to August 2009. Other rheumatologic disorders, atherosclerotic or cardiogenic stroke, multiple sclerosis, septic meningitis, acquired immune deficiency syndrome, and other major differential diagnoses were ruled out. In addition to Cs and immunosuppressive drugs, they might be received colchicines or sulfasalazine. Off-label usage of INFX was thoroughly explained to the patients and written informed consent was taken. Heart failure, liver abnormalities, and tuberculosis and other active infections were excluded before administration of INFX.

INFX 3 or 5 mg/kg was administered by intravenous infusion at weeks 0, 2, 6, and every 8 weeks then. No infusion reaction was seen. Severe leucopenia (absolute granulocyte count less than 1,500) or increase liver enzymes (>3 times to base line) were not seen. Demographic and clinical characteristics of patients, clinical and radiological response to INFX, and adverse drug reactions (ADRs) were summarized in Table 1.

Patient 1

The patient was a 28-year-old male with 11-year history of BD referred with fever, headache, right-sided weakness, decreased level of consciousness for 4 days. Brain MRI revealed an extending lesion in posterior limb of left internal capsule and thalamus with extension to cerebral peduncle, midbrain, pons, and upper medulla associated with a few small white matter lesions. He improved with intravenous methylprednisolone (IVMP) 1 g/day for 7 days; and then prednisolone (PDSN) 75 mg/day tapered to 5 mg/day. Firstly, pulsed cyclophosphamide (CTX) 500 mg IV monthly was started. But he had three attacks of fever, headache, weakness, and incontinence in next 2 years. Therefore, INFX 3 mg/kg was added to CTX and low-dose PDSN. The patient improved to some degree after the first administration of INFX. Follow-up MRI showed diminishment of the previous extending lesion but evolution of other small lesions in both thalami and left frontal periventricular area. Despite initial promising results, he had a progressive course of neurological deficits with dementia, parapresis, and incontinence (pseudobulbar palsy). In last attack, the patient developed drowsiness, stupor and then coma, and passed away.

Patient 2

The patient was a 43-year-old male with BD for 9 years who referred with progressive spastic quadriparesis, dementia, and incontinence after one episode of stroke-like manifestations. Brain MRI showed several medium-sized hypersignal lesions in periventricular and centrum semiovale, midbrain and pons. Monthly pulses of CTX (500–1,000 mg) were administered for 9 months and PDSN (30–2.5 mg/day) for 3 months. Due to unsatisfactory response, INFX (5 mg/kg) was added to CTX. Weakness, mental activity, and incontinence improved gradually. Brain MRI also revealed diminishment in size and number of the lesions.

The patient received cumulative dose of 1,200 mg, but he could not afford the drug then. After discontinuation of INFX, he had been attack-free on monthly CTX (500 mg/month) and then methotrexate (MTX) 12.5 mg/week and PDSN 5 mg/day. In last follow-up, 16 months after INFX initiation, he had no motor or urinary disability but mild mental disorder.

Patient 3

A 37-year-old man presented with acute confusional state, weakness, corticopspinal signs and bilateral diamesencephalic lesions in the brain MRI. He had recurrent oral and genital ulcers and acne-like lesions before, but diagnosis of BD had been neglected. Pathergy reaction was positive. His level of consciousness improved by IVMP 1 g/day for 7 days; and then PDSN 60 mg/day tapered to 30 mg/day. Due to severity of clinicoradiological manifestations, it was decided that INFX (5 mg/kg) and CTX (1,000 mg IV monthly) to be started from the beginning. He improved according to mental and motor activities and size of MRI lesions. But he refused to continue INFX due to financial problems.CTX and PDSN were continued with same schedule. He had mild motor and mental disability in 11-month follow-up.

Table 1 Demographic and clinical characteristics of the patients and dose, therapeutic effects and adverse drug reaction of infliximab in current four patients

	Patient 1	Patient 2	Patient 3	Patient4
Sex	M	M	M	M
Ethnicity	Iranian	Iranian	Iranian	Iranian
Age at time of IFNX administration (year)	39	43	39	41
Duration of BD/NBD at time of IFNX administration (year)	11/2	9/2	neglected	12/2
General BD manifestation	ROU, RGU, Uv, +Path	ROU, RGU, Uv	ROU, RGU, Cut, +Path	ROU, RGU, Cut, +Path
Type of NBD before IFNX administration (relapsing-remitting/ primary progressive/secondary progressive)	RP	SP	PP	SP
Treatments before IFNX	Cs, Col, SSZ,CTX	CS, Col, CTX	NA	CS, Col, CTX
Administered IFNX Brand	Ramicade	Ramicade	Ramicade	Ramicade
Dose (mg/kg/each infusion)	3	5	5	3
Duration of treatment (weeks)	22	22	14	22
Adjuvant treatments (immunosuppressive, corticosteroids)	Cs, CTX, Col	CTX, Col	Cs, CTX, Col	Cs, Col
Initial clinical response (/? 1 month after first infusion)[a]	+	++	++	++
Initial radiological response[b]	+	+	++	++
Eventual clinical response[a]	0	++	+	0
Adverse drug reactions	−	−	−	Varicella zoster infectio
Follow-up	Deceased after 3 years	Mild mental disorder with CS and MTX(16 months)	Mild motor and mental disability with CS,CTX (11 month)	Deceased after 2 years

ROU recurrent oral ulcers, *RGU* recurrent genital ulcers, *Uv* uveitis, *Cut* cutaneous manifestations, *+Path* positive pathergy reaction, *RP* relapsing progressive, *PP* primary progressive, *SI* secondary progressive, *CS* corticosteroids, *Col* colchicine, *CTX* cyclophosphamides, *SSX* sulfasalazine, *IFNX* infliximab, *NA* not applicable

[a] +++ no remained NBD symptoms and signs, and significant recovery of function; ++ mild remained NBD symptoms, and pause of progression; + remained NBD symptoms and signs, and slowe progression in PP patients; *0* no change; − new relapse(s) or more severe progression

[b] +++ disappearance of T2WI lesions and loss of contrast enhancement; ++ >50% decrease in number and size of T2WI lesions and loss of contrast enhancement; + <50% decrease in number and size o T2WI lesions and loss of contrast enhancement; *0* no change; − increase in number and size of T2WI lesions or persistent contrast enhancement

Patient 4

A 41-year-old man who has been reported before [6].

Review of article

In 2003, Licata et al. reported a 59-year-old woman with relapse of the NBD in spite of monthly IVMP and CTX. The patient was infused with INFX 5 mg/kg intravenous infusion at weeks 0.2 and 6. Her symptoms improved within 24 h after fist infusion. Brain MRI revealed complete resolution of signal abnormalities too. She was stable in 1 month's follow/up [7].

In 2005, Sarwar et al. reported a Palestinian man with incomplete form of BD who had multifocal enhancing lesions in brain MRI and vasculitis pattern in brain biopsy. He showed a remarkable response to three doses of 3 mg/kg intravenous infusion of INFX. After TNF blockade therapy, they were able to taper Cs for the patient [8].

In 2005, Ribi et al. reported a patient with NBD who relapsed in spite of being treated with pulsed CTX and Cs. INFX at a dose of 5 mg/kg was added to previous drugs. He showed partial clinical improvement and regression of brain MRI lesions. Seven months after discontinuation of IFNX, he developed another relapse which was treated with new infusion of IFNX. The patient's neurological deficit, presented since the first episode and exacerbated by subsequent relapses, persisted in spite of INFX administration [9].

Alty et al. (2007), described a patient with longstanding NBD who was poorly responsive to AZT, CsA, MTX and thalidomide. She responded extremely well to bimonthly infusion of 3 mg/kg INFX. But they were obligated to switch to etanercept due to hepatotoxicity. The patient showed a remarkable response to twice-weekly subcutaneous injections of 25 mg etanercept too [10].

In 2007, Fujikawa et al., described a patient with refractory NBD successfully treated by INFX [11].

In 2008, Belzunegui et al. presented a young man with NBD refractory to CTX, AZT, and Cs. They treated the patient with INFX 3 mg/kg just for four doses. After initial improvement, they shifted to AZT and Cs, but NBD flared again [12].

In Pipitone et al. study (2008), IFNX induced clinical and radiological remission as an adjuvant therapy to Cs, MTX, and/or CsA in seven out of eight Italian patients with refractory NBD. No severe adverse drug effect was seen among their patients [13].

In 2008, Madanat and Madanat reported a patient with NBD refractory to AZT, CsA, and CTX. She had a good response to combination of INFX (5 mg/kg) and MTX (10 mg/week) but her pre-existing osteomalacia relapsed with infusions of INFX [14].

Table 2 Demographic and clinical characteristics of the patients and dose, therapeutic effects, and adverse drug reaction of infliximab in previous reports

Name	Year	Country	No[a]	Age/sex	Adjuvant drug	Dose	Course	Short-term response	Midterm response	ADR
Licata et al.	2003	Italy	1	59/F	NM	5 mg/kg	Weeks 0.2,6	Good	NM	–
Sarwar	2005	USA[#]	1	42/M	Cs	3 mg/kg	3 doses	Good	Good	–
Ribi et al.	2005	Switzerland	1	23/M	CTX,Cs and then AZT,Cs,	5 mg/kg	1 year, and then 16 months	Good	Fair	–
Fujikawa et al.	2007	Japan	1	36/F	Cs	3 mg/kg	Weeks 0.2,6	Good	NM	–
Alty et al.	2007	UK	1	39/F	MTX	3 mg/kg	3 years	Good	Good	Hepatotoxicity
Pipitone at al.	2008	Italy	8	Mean 40.1/6 M;2 F	Cs, MTX,or CsA	5 mg/kg	1–3 year(s)	Good:8/8	Good 7/8	–
Kikuchi et al.	2008	Japan	5	Mean:35.6/5 M	MTX,Cs	5 mg/kg	4 years	Good 5/5	Good 3/5	Transient headache, suspected subclinica pneumocystic pneumonia
Madanat and Madanat	2008	Jorda	1	49/F	MTX	5 mg/kg	NM	Good	NM	Worsening of osteomalacia
Ablos-Medina et al.	2009	Spain	1	52/F	MTX	5 mg/kg	1 year	Good	Good	–
Matsui et al.	2010	Japan	1	29/M	MTX,Cs	5 mg/kg	2 years	Good	Fair	–
Al-Araji et al.	2010	Ten countries	18	Mean 29.4/12 M;6 F	NM	5 mg/kg	Mean; 20.9 months	NM	Good 17/18	CNS demyelinization in 1/18
Current series	2011	Iran	4	Mean 40.5/4 M	See Table 1	3 or 5 mg/kg	Median 22 weeks	Good:4/4	Good:2/4	Varicella zoster in 1/4

M male, *F* female, *ADR* adverse drug reaction, *NM* not mentioned, *Col* colchicines, *Cs* corticosteroids, *AZT* azathioprine, *CTX* cyclophosphamide, *CsA* cyclosporine A, *MTX* methotrexate+

[a] Palestinian originally

In Kikuchi et al. study (2008), INFX (5 mg/kg/day) was added to MTX in five patients with progressive NBD. Neuropsychiatric and radiological outcomes were, overall, satisfying. Interestingly, the therapeutic effect of INFX was paralleled with reduction in CSF IL-6 levels but not TNF-alpha [15]. This center presented 4-year follow-up in these patients, which was favorable in three out of five patients [16].

In 2009, Abalos-Medina et al. treated a refractory NBD patient with INFX 5 mg/kg and MTX 15 mg weekly. The patient had a dramatic clinical and radiological improvement and remained attack-free with INFX [17].

In one of Matsui et al. (2010) patients, attack of acute NBD during the chronic progressive course responded well to IFNX (5 mg/kg) and MTX, clinically, radiologically, and according to CSF IL-6 level. But this regimen could not stop the progressive course.CSF IL-6 returned to high levels too [18].

Al-Araji et al. (2010) presented the largest series of NBD patients on INFX with mean treatment of duration of 20.9 months. Favorable outcome was seen in 17 out of 18 patients. Central nervous system (CNS) demyelination as a major ADR was seen in one patient [19].

Sfikakis et al. (2007) recommended INFX for NBD patients refractory to treatment with pulsed CTX and PDSN, or AZT and PDSN [20].

In Alpsoy and Akman(2009) algorithmic approach to different NBD manifestations, anti-TNF-alpha drugs were considered for patients refractory to CTX and Cs with or without AZT [21].

Borhani Haghighi and Safari (2010) proposed a therapeutic algorithm for NBD. INFX or other anti-TNF-alpha drugs should be kept for low-risk patients refractory to two stages of immune-suppressant therapy or high-risk patients refractory to one stage of immune-suppressants [22].

Discussion

Our results with INFX were not as promising as the previous reports. Collectedly, 33 out of 39 (84.6%) of abovementioned reports had good clinical results.(Table 2) CNS-specific response in a review of anti-TNF agents for general BD was 83% [4]. The issue of publication bias should be kept in mind. In our study, clinical responses were unsatisfactory for two patients on 3 mg/kg regimen; and good in two patients on 5 mg/kg regimen.

Monotherapy versus combination therapy is another concern. In prospective studies with more than five patients, sustained response to INFX was seen in 4/5 patients on monotherapy, 1/1 on INFX+CsA, and 5/5 on IFNX+MTX [4]. In current series, the patients who receive 5 mg/kg dose INFX and monthly CTX pulses had better clinical and radiological responses too.

High cost of the drug made two patients to discontinue the drug. The issue of the cost should be highly considered in developing countries. A remission-induction course anti-TNF drug+immunosuppressive, which replaced by immunosuppressive alone, can be a resolution. This policy was effective in some previous reports [8, 11] but not in the others [9].

Varicella zoster infection, which was seen in one of our patients, has also been reported in another patient of BD on IFNX.[23] Other major reported ADRs such as tuberculosis and other opportunistic infections [4], evolution of lymphoma [4], worsening of osteomalacia [14], and hepatotxicity [10] were not seen in our patients. CNS demyelinization has been reported in one patient of Al-Araji series [19]. Differential diagnosis from NBD per se with multiple sclerosis-like manifestations [24] is crucial.

As shortcomings, we did not measure serum and CSF IL-6 and TNF-alpha and anti-infliximab antibodies in our patients. Follow-up duration was also relatively short in the last two patients.

Of patients with parenchymal NBD, 35%, 28%, and 20.4% entered a progressive course in large Turkish [25], Japanese [26], and Iranian series [unpublished data], respectively. In a 7-year longitudinal study, we have recently shown incremental pattern in the number of lesions and MRI burdens in patients with parenchymal NBD despite currently available treatments [24]. It necessitates selection of more efficacious regimens. Current case series and literature review show INFX with adjuvant immunosuppressive drug and tapering doses of Cs, if administered in early course of progressive NBD, can be helpful. But it is not the magic bullet.

Disclosures None

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