
Infliximab in refractory uveitis due to Behçet's disease

B. Wechsler¹, R. Sablé-Fourtassou¹, B. Bodaghi², D.L.T. Huong¹, N. Cassoux²,
I. Badelon⁴, O. Fain³, P. LeHoang², J.-C. Piette¹

¹Department of Internal Medicine and

²Department of Ophthalmology Hôpital Pitié-Salpêtrière, Paris; ³Department of Internal Medicine and ⁴Department of Ophthalmology, Hôpital Jean Verdier, Bondy, France.

Bertrand Wechsler, MD; Régis Sablé-Fourtassou, MD; Bahram Bodaghi, MD; Du Lê Thi Huong, MD; Nathalie Cassoux, MD; Isabelle Badelon, MD; Olivier Fain, MD; Phuc LeHoang, MD; Jean-Charles Piette, MD.

Please address correspondence to: Bertrand Wechsler, MD, Department of Internal Medicine, Hôpital Pitié-Salpêtrière, 75013 Paris, France.

Received on March 10, 2003; accepted in revised form on October 3, 2003.

Clin Exp Rheumatol 2004; 22 (Suppl. 34): S14-S16.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2004.

Key words: Behçet's disease, uveitis, anti-TNF, infliximab.

ABSTRACT

Objective. To report 4 cases of refractory panuveitis due to Behçet's disease treated with a novel therapy: infliximab.

Methods. Retrospective study of 3 women and 1 man of Caucasian origin with Behçet's disease complicated with panuveitis. Their uveitis was relapsing from 48 to 96 months and was resistant to the combination of colchicine (n = 4), high-dose prednisone (n = 4), pentoxifylline (n = 2) and various immunosuppressors and/or immunomodulators given successively: intravenous cyclophosphamide (n = 4), azathioprine (n = 3), interferon alpha (n = 3), cyclosporine A (n = 2), oral cyclophosphamide (n = 1), mycophenolate mofetil (n = 1), methotrexate (n = 1), high-dose immunoglobulin (n = 1). Combination with respectively 1, 3, 4 and 5 immunosuppressors and/or immunomodulators failed before institution of infliximab. After informed consent was obtained, infliximab was administered as a single infusion of 5 mg/kg (maximum dose: 400 mg) at day 1, at week 2, 6 and then every 8 weeks.

Results. With a follow-up ranging from 7 to 22 months, infliximab was efficient in all cases. The mean prednisone dose decreased from 45 mg to 13 mg daily. Total recovery of visual acuity was observed in half of the cases. Infliximab was well tolerated without fever, severe sepsis or autoimmune manifestation.

Conclusion. Infliximab may be efficient in refractory uveitis due to Behçet's disease. The optimal dose, rhythm and duration of infliximab infusions need to be standardized.

Introduction

Behçet's disease (BD) is a vasculitis of unknown origin and its pathogenesis remains unclear. However, concentrations of tumour necrosis factor (TNF)

and soluble TNF receptors are increased in the serum of patients with active disease (1-3). Recent reports demonstrated that infliximab, a chimeric monoclonal antibody directed against TNF-alpha, was beneficial in resistant uveitis due to BD (4, 5). We report our experience with 4 cases of panuveitis due to BD and resistant to conventional therapy. In each case, after informed consent was obtained, infliximab was administered as a single 2-hour intravenous (i.v.) infusion of 5 mg/kg (maximum 400 mg) at day 1, week 2, 6 and then maintained every 8 weeks.

Uveitis was diagnosed in a tertiary eye care centre. Visual acuity was evaluated in all cases. The severity of ocular inflammation was estimated after slit lamp and fundus examinations. Anterior uveitis involved the iris and the ciliary body whereas posterior uveitis presented with retinal vasculitis, foci of retinal necrosis, papillitis and macular edema. Vitritis was present in all patients. The association of anterior uveitis, vitritis and posterior uveitis was considered as a panuveitis. Laser flare photometry (KOWA 1000, Japan) was performed in all cases in order to quantify the level of anterior chamber inflammation. Fluorescein angiography was performed initially and during the follow-up to evaluate the efficacy of infliximab.

Case reports

Case n° 1

A Caucasian woman born in 1963 presented in 1994 with uveitis, arthritis, and bipolar aphthae. HLAB5 was present. Several relapses of panuveitis including anterior uveitis, vitreous haze and retinal necrosis occurred despite a combination of prednisone, colchicine and pentoxifylline, in addition to various immunosuppressors or immunomodulators successively administered: i.v. cyclophosphamide (24 pulses), aza-

thioprine withdrawn after acute hepatitis, and interferon alpha-2a discontinued because of depression. In June 2001 her right visual acuity decreased from 20/25 to 20/200 because of a severe episode of panuveitis associating vitritis, retinal vasculitis, macular edema and papillitis.

Infliximab was started after 3 i.v. pulses of 1 g methylprednisolone. Twenty-two months later no recurrence was observed. Only few spots of cutaneous pseudofolliculitis persisted. The prednisone dose was progressively tapered from 30 mg to 7 mg daily and her visual acuity increased to 20/25. In October 2002 methotrexate (10mg weekly) was added in order to delay the infusions to every 10, and then every 12 weeks.

Case n° 2

A Caucasian man born in 1968 presented in 1997 with dural sinus thrombosis, bipolar aphthae and bilateral uveitis. HLA B5 was absent. In this poorly compliant patient, recurrent relapses of left panuveitis with retinal necrosis occurred despite prednisone, colchicine, pentoxifylline and i.v. cyclophosphamide (22 pulses). Steroids induced bilateral hip necrosis. In September 2001 a severe relapse of right posterior uveitis decreased visual acuity to 20/200. Infliximab was started after 3 pulses of 1 g methylprednisolone followed by 60 mg daily prednisone. Interferon alpha and azathioprine were contraindicated because of prior poor compliance. His visual acuity increased rapidly to 20/20. Five months later, a mild anterior segment inflammation was present, but subsequently vanished. At the 12-month follow-up the prednisone dose could be tapered to 10 mg daily. In May 2003 methotrexate (15 mg weekly) was added when a moderate relapse of posterior uveitis occurred.

Case n° 3

A Caucasian woman born in 1980 was referred for BD resistant to therapy. The diagnosis of BD was made in 1993 on the basis of bilateral panuveitis, bipolar aphthae and arthritis. HLAB5 was present. Several relapses of panuveitis occurred despite a combination of colchicine and prednisone and the

successive use of azathioprine (100 mg daily), cyclosporin A (350 mg daily), interferon alpha-2a (3 to 6 million units thrice a week) and i.v. cyclophosphamide leading to right enucleation. In June 2001, after the third cyclophosphamide pulse, left uveitis relapsed associated with right transient hemiplegia. Cerebral magnetic resonance imaging was normal. Despite 3 pulses of 1 g methylprednisolone followed by 25 mg daily prednisone, her visual acuity decreased to 20/40.

Cyclophosphamide was stopped and infliximab was started. In September 2001, her visual acuity improved to 20/20. Worth noting is the observation that when the 6th and 8th infliximab infusions were delayed due to genital herpes recurrence and a transient pulmonary infection, respectively, a mild flare-up occurred which rapidly subsided with topical steroids. With a 22-month follow-up, there were no other recurrences, in particular of the neurological symptoms, and prednisone could be tapered to 9 mg daily. In March 2003 methotrexate (7.5 mg/week) was added.

Case n° 4

A Caucasian woman born in 1971 presented in 1977 with uveitis, oral aphthae, uveitis and erythema nodosum. HLA B5 was present. Several relapses of bilateral panuveitis occurred despite a combination of colchicine and prednisone and the successive use of methotrexate (10 mg/week), azathioprine (150 mg daily), cyclosporine A (200 mg daily), mycophenolate mofetil (2 g daily), i.v. cyclophosphamide (6 pulses), oral cyclophosphamide (2 mg/kg daily), i.v. immunoglobulin and interferon alpha-2a. In October 2001, despite 30 mg daily prednisone her right visual acuity decreased from 60/200 to 20/200 due to severe posterior uveitis including retinal necrosis, papillitis, diffuse retinal vasculitis and cystoid edema. Infliximab was started. At the 7-month follow-up, no recurrence was observed and her right visual acuity had improved to 40/200. The prednisone dose could be tapered to 25 mg daily.

Discussion

All these cases of panuveitis due to BD

were refractory to the combination of colchicine, high-dose prednisone and immunosuppressors and/or immunomodulators. Azathioprine and cyclophosphamide were tried in all patients, interferon alpha in 3, cyclosporine in 2, methotrexate and mycophenolate mofetil in one patient each, respectively. Combination with respectively 1, 3, 4 and 5 immunosuppressors and/or immunomodulators failed before the institution of infliximab.

Infliximab was initiated after the disease had been active for 48 to 96 months. Infliximab may be considered to have been efficient in all cases since: 1) the prednisone dose could be tapered from a mean dosage of 45 mg (range: 65 to 25) to 11 mg daily (range: 18 to 7) (discontinuation of steroids was not attempted); 2) an improvement was seen in the visual acuity of the involved eye in each of the patients, and a completely recovery in 2 eyes with 20/20 visual acuity; 3) with a follow-up of 7 to 22 months (mean:15) only mild relapses were seen after the institution of infliximab, although methotrexate had to be secondarily associated in 3 cases.

Although this was not a controlled study, choosing patients refractory to a combination of high-dose steroids and immunosuppressors rules out the possibility of an overestimation of the benefit of the drug. Infliximab was also well tolerated. We did not observe fever, severe sepsis or autoimmune manifestations. Genital herpes and transient pulmonary infection occurred in case n° 3 but it resolved rapidly with antiviral or antibiotic therapy. Nevertheless, infliximab seemed to be only suspensive since mild ocular relapses were observed in 2 patients.

Recent anecdotal reports or small series have emphasized the beneficial effect of infliximab on various BD manifestations. Goosens (6) reported a one-year remission of mucocutaneous manifestations after 2 infusions of 700 mg infliximab in a patient with oral and ano-genital aphthous ulcerations resistant to various immunosuppressive regimens. Robertson (7) reported remission of mucocutaneous ulcerations and arthritis resistant to thalidomide, disulfone, azathioprine, colchicine and cy-

cyclosporin after 3 infliximab infusions in a 65-year-old woman. Rozenbaum (8) reported a similar experience in a 47-year-old patient. Travis (9) reported 2 cases of gastro-intestinal BD treated with infliximab. In the first patient, sigmoid colon abscess and perianal fistula resistant to steroids and thalidomide remitted after 2 infliximab infusions with 17-month follow-up. The second patient had colonic ulcers resistant to prednisone and cyclosporine, which improved after the first 5 mg/kg infliximab infusion. Relapse required the administration of infusions at weeks 52 and 64 without complications. Hassard (10) reported a case of long-lasting cortico-dependant digestive BD in which steroids could be stopped after 2 infliximab infusions; remission persisted after infusions at week 7 and 23. Fresno (11) reported an unusual gastroparesia attributed to BD, which dramatically improved with a 11-month follow-up after infusions of 300 mg infliximab performed every 8 weeks, in addition to methotrexate and disulone. Even if gastrointestinal BD involvement is difficult to differentiate from ulcerative colitis, a disease for which anti-TNF therapy is clearly indicated after the failure of immunosuppressors, the improvement in these patients appeared clinically relevant. To our knowledge, the beneficial effect of infliximab was previously reported in 11 BD patients with uveitis, some cases being reported only as abstracts and some others in which immunosuppressors were maintained. Banares (4) reported improvement of visual acuity in 5 out of 7 patients with resistant BD uveitis after 5 mg/kg infliximab infusion performed at weeks 0, 2 and 6. Sfikakis (5) reported improvement of resistant BD uveitis in 5 patients treated with 5 mg/kg infliximab in addition to prednisone (n = 5), cyclosporine (n = 5) and azathioprine (n = 3). Improvement was observed as early as in the first 24 hours in one patient, and in less than one week for the others. Mucocutaneous manifestations concurrently improved in 2 patients and the arthritis present in one

patient remitted in 4 days. Munoz-Fernandez (12) reported the improvement of a patient with bilateral BD uveitis refractory to corticosteroids, methotrexate and cyclosporin after 5 mg/kg infliximab infusions at weeks 0, 2 and 6. Hence, despite the lack of controlled trials, infliximab appears to be effective against the mucocutaneous, gastrointestinal and ocular manifestations of BD. More recently Licata *et al.* reported a complete remission of cerebral vasculitis in a 59-year-old woman who relapsed despite i.v. methylprednisolone and cyclophosphamide (13). In our case n° 3, hemiplegia improved with infliximab. It must be noted, however, that neurological side effects such as demyelination (14, 15) and aseptic meningitis (16) have been reported with anti-TNF and hence infliximab should be used with special care in neurological BD. The risk of reactivation of infection, especially tuberculosis, is also a great concern in populations where the prevalence of BD is high, such as along the "Silk Road" (17). Due to its present high cost, it is difficult to consider infliximab as a long-term therapy for chronic disease. Due to its rapidity of action, one possibility may be to administer the drug earlier in the course of the disease in order to spare steroids and facilitate the action of other immunosuppressive agents. In conclusion, infliximab is efficient in refractory uveitis due to Behçet's disease after the failure of classical immunosuppressors and/or immunomodulators. However the optimal dose, rhythm and duration of infliximab infusions need to be standardized.

References

1. SAYINALP N, OZCEBE OI, OZDEMIRO, HAZNEDAROGLU IC, DUNDAR S, KIRAZLI S: Cytokines in Behçet's disease. *J Rheumatol* 1996; 23: 321-2.
2. MEGE JL, DILSEN N, SANGUEDOLCE V *et al.*: Overproduction of monocyte derived tumor necrosis factor alpha, interleukin (IL) 6, IL-8 and increased neutrophil superoxide generation in Behçet's disease. *J Rheumatol* 1993; 20: 1544-9.
3. TURAN B, GALLATI H, ERDI H, GURLER A, MICHEL BA, VILLIGER PM: Systemic levels of T cell regulatory cytokines IL-10 and IL-12 in Behçet's disease: soluble TNF R-75 as a biological marker of disease activity. *J Rheumatol* 1997; 24: 128-32.
4. BANARES A, ABASALO L, MACARRON P *et al.*: Treatment of refractory posterior uveitis with anti-TNF-alpha (Infliximab). *Arthritis Rheum* 2001; 44: S90-227.
5. SFIKAKIS PP, THEODOSSIADIS PG, KATSIARI CG, KAKLAMANIS P, MARKOMICHELAkis NN: Effect of infliximab on sight-threatening panuveitis in Behçet's disease. *Lancet* 2001; 358: 295-6.
6. GOOSSENS PH, VERBURG RJ, BREEDVELD FC: Remission of Behçet's syndrome with tumour necrosis factor alpha blocking therapy. *Ann Rheum Dis* 2001; 60: 637.
7. ROBERTSON LP, HICKLING P: Treatment of recalcitrant orogenital ulceration of Behçet's syndrome with infliximab. *Rheumatology* 2001; 40: 473-4.
8. ROZENBAUM M, ROSNER I, PORTNOY E: Remission of Behçet's syndrome with TNFalpha blocking agent. *Ann Rheum Dis* 2002; 61: 283-4.
9. TRAVIS SPL, CZAJKOWSKI M, MCGOVERN DP, WATSON RG, BELL AL: Treatment of intestinal Behçet's syndrome with chimeric tumour necrosis factor alpha antibody. *Gut* 2001; 49: 725-8.
10. HASSARD PV, BINDER SW, NELSON V, VASILIAUSKAS EA: Anti-tumour necrosis factor monoclonal antibody therapy for gastrointestinal Behçet's disease: a case report. *Gastroenterology* 2001; 120: 995-9.
11. FRESNO RB: Behçet's disease associated with severe gastroparesis: a dramatic response to combination therapy with methotrexate and infliximab. *Arthritis Rheum* 2001; 44: S120-408.
12. MUNOZ-FERNANDEZ S, HIDALGO V, FERNANDEZ-MELON J, SCHLINCKER A, MARTIN-MOLA: Effect of infliximab on threatening panuveitis in Behçet's disease. *Lancet* 2001; 358: 1644.
13. LICATA G, PINTO A, TUTTOLOMENDO A *et al.*: Anti-tumour necrosis factor alpha monoclonal antibody therapy for recalcitrant cerebral vasculitis in a patient with Behçet's syndrome. *Ann Rheum Dis* 2003; 62: 280-1.
14. MOHAN N, EDWARDS ET, CUPPS TR *et al.*: Demyelination occurring during anti-tumour necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* 2001; 44: 2862-9.
15. VAN OOSTEN BW, BARKHOFF F, TRUYEN L: Increased MRI activity and immune activation in two multiple sclerosis patients treated with the monoclonal anti-tumour necrosis factor antibody cA2. *Neurology* 1996; 47: 1531-4.
16. MAROTTE HCJ, MIOSECC P: Infliximab-induced aseptic meningitis. *Lancet* 2001; 358: 1784.
17. KEANE J, GERSHON S, WISE RP *et al.*: Tuberculosis associated with Infliximab, a tumor necrosis factor neutralizing agent. *N Engl J Med* 2001; 345: 1098-104.