Jpn J Ophthalmol 2007;51:191–196
DOI 10.1007/s10384-006-0425-y

CLINICAL INVESTIGATION

Infliximab Treatment for Ocular and Extraocular Manifestations of Behçet's Disease

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Abstract

Purpose: To assess the efficacy and safety of infliximab in the treatment of sight-threatening uveitis and extraocular manifestations in patients with Behçet's disease.

Methods: Twelve patients with Behçet's disease and uveitis were treated with infliximab after unsuccessful therapy with other immunosuppressive drugs. The main outcome measures were as follows: the number of uveitis relapses, the number of Behçet's disease-related extraocular lesions, and the amount of corticosteroids administered during the treatment as well as during an equal prior period of time while the patients were on other immunosuppressive agents. Visual acuity was recorded at the beginning of infliximab therapy and at the end of follow-up, and was defined as stable if it did not change from baseline, increased if it showed at least one line of improvement from baseline, and decreased if it showed at least a one line decrease from baseline.

Results: During an average follow-up of 16.67 ± 7.63 months (median, 15 months), 11 patients (91.6%) showed a reduction in the number of ocular relapses (relapse/month, from 0.35 ± 0.17 to 0.12 ± 0.17, $P < 0.001$). All of the patients ($n = 11$) who were taking corticosteroids before infliximab were able to reduce the amount of corticosteroids taken daily during infliximab treatment (from 24.33 ± 10.84 mg/prednisone per day to 8.97 ± 6.81 mg/prednisone per day, $P < 0.001$), and all presented with a reduced onset of extraocular manifestations of Behçet's disease (mean total number, from 2.83 ± 3.61 to 1.51 ± 2.35, $P = 0.039$). One patient, who had to stop treatment 2 months after starting because of the onset of pulmonary tuberculosis, showed the same number of relapses during infliximab treatment but was able to reduce the mean daily corticosteroid dose. Visual acuity increased by one or more lines in three eyes (12.5%) and remained unchanged in 87.5% of the eyes. Infliximab-related side effects appeared in four patients (33.3%).

Conclusions: Infliximab was effective in the treatment of uveitis in these Behçet's disease patients, significantly reducing the number of ocular relapses and making possible a significant reduction in the daily dose of corticosteroids administered. Extraocular manifestations of Behçet's disease were also controlled by infliximab. Nevertheless, side effects were not uncommon, and an extensive study of systemic conditions before infliximab administration had to be carried out to exclude systemic infection, particularly prior tuberculosis. **Jpn J Ophthalmol** 2007;51:191–196 © Japanese Ophthalmological Society 2007

Key Words: anti-TNFα therapy, Behçet's disease, infliximab, uveitis

Introduction

Behçet's disease (BD) is a systemic vasculitis characterized by the onset in young adults of recurrent oral and genital ulcers, skin lesions, and uveitis. In the first description by Behçet,[1] anterior uveitis with hypopyon was the typical ocular lesion. Nowadays, a predominant posterior or diffuse

Received: May 10, 2006 / Accepted: December 20, 2006
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uveitis with retinal vasculitis is the main feature of this disease. Therefore, the ocular lesions often may be sight-threatening, requiring very aggressive treatment to try to preserve useful visual acuity.[2,3] Immunosuppressive therapy is the mainstay of treatment of BD-related ocular lesions, but despite intensive therapy, some patients may display progressive occlusive vasculitis with loss of vision.[4] The etiology of BD is still unknown, but it is known that T lymphocytes play an important role in its development by releasing cytokines, which stimulate a cascade of events resulting in damage to the targeted tissues.[5]

Tumor necrosis factor alpha (TNFα) is a proinflammatory cytokine. Increased concentrations of TNFα and of its soluble receptors have been detected in the serum of BD patients with active disease.[6] Furthermore, TNFα has also been detected in a significant concentration in the aqueous humor of patients with uveitis.[7,8] Recent reports have indicated that anti-TNFα therapy may be beneficial in the management of ocular and extraocular lesions in BD patients.[9–19] Infliximab (Remicade; Schering Plough, Segrate, Milan, Italy), a humanized mouse monoclonal antibody against TNF, is currently used in the treatment of rheumatoid arthritis and Crohn's disease.[20–22] Infliximab neutralizes the biologic activity of TNF by binding to the soluble and membrane-bound forms of TNF.[23]

The aim of this study was to assess the efficacy and side effects of infliximab in BD patients with sight-threatening uveitis.

Patients and Methods

We included in this study 12 patients with Behçet's disease, nine men and three women, average age, 34.51 ± 5.98 years (range, 25–45 years) observed at the Servizio di Immunovirologia Oculare, Dipartimento di Scienze Oftalmologiche, Università degli Studi di Roma "La Sapienza", Rome, Italy. The diagnosis of Behçet's disease was formulated according to the criteria established by the International Study Group for Behçet's disease.[24]

Eleven of the patients suffered from recurrent diffuse uveitis with retinal vasculitis, and one from recurrent anterior uveitis and diffuse necrotizing scleritis. Before being included in the study, seven patients had been treated with immunosuppressive therapy (either cyclosporine A 5 mg/kg per day, azathioprine 100 mg/day, methotrexate 15–20 mg/week, chlorambucil 0.1–0.2 mg/kg per day, colchicine 1 g/day, or interferon α 3 million units three times/week, or a combination of these drugs) and corticosteroids. One patient had received immunosuppressive therapy and nonsteroidal anti-inflammatory drugs (NSAIDs) because of osteonecrosis in the ankles and knees.

All of the patients were followed up by us at least monthly for 1 year before being included in the study and were considered either unresponsive or poorly responsive to the standard therapy, showing at least two recurrences in the last year of the above-reported treatment. After a complete work-up, including testing for complete blood count, erythrocyte sedimentation rate, chest X-ray, purified protein derivative (PPD), urinalysis, kidney and liver function, C-reactive protein, and autoimmune antibodies (nucleus, dsDNA, antineutrophil cytoplasmic) and after informed consent was obtained, all patients were treated with infliximab intravenously at a dose of 5 mg/kg at time 0, after 14 days, monthly for an additional 4–6 months or according to the clinical response, and every 45–60 days thereafter.

All patients received infliximab while no ocular or extraocular lesions were present. The daily corticosteroid dose was gradually tapered according to the clinical course of the disease, considering both the ocular and the extraocular symptoms of Behçet's disease. Previously, immunosuppressive therapy had been stopped in six of the patients, and the others were receiving methotrexate 15 mg/week parenterally or azathioprine 50 mg/day orally. All patients were examined at days 7, 14, and 21 after infliximab initiation and then monthly, unless otherwise indicated by the clinical course of the disease. The number of uveitis recurrences, the mean daily steroid dose administered for any reason to the patients, and any extraocular lesions that occurred during an equal period of time before and while on infliximab therapy were recorded and reported as means ± SD. Visual acuity at the beginning of infliximab therapy and at the end of follow-up was recorded and considered stable if it did not change by at least one line from baseline, increased if it showed at least one line of improvement, and decreased if it showed at least one line of decrease.

During infliximab therapy the following examinations were performed every 3 months: complete blood count, erythrocyte sedimentation rate, kidney and liver function, C-reactive protein, urinalysis, and autoimmune antibodies, as was done before infliximab administration.

The reported parameters were compared between equal periods of time before and while on infliximab therapy. The Student t test for paired data was used for statistical analysis. P values lower than 0.05 were considered statistically significant.

Results

Table 1 reports the ocular features of the patients before and during infliximab therapy. The mean follow-up of the patients after initiation of infliximab was 16.67 ± 7.63 months (range, 2–30 months; median, 15 months). All patients but one (11 cases, 91.6%) showed a reduction in the number of relapses per month of therapy, and the mean relapses per month decreased significantly from 0.35 ± 0.17 to 0.12 ± 0.17 ($t = 5.647$, $P < 0.001$). The only patient who did not show a reduction in the number of relapses between before and during treatment with infliximab was the one who had to stop therapy because of the onset of pulmonary tuberculosis 2 months after starting infliximab (after three infusions). Before starting therapy he had displayed a negative chest X-ray and unremarkable PPD. However, at the time of PPD testing the patient was on cyclosporine A 5 mg/kg per day, colchicine 1 g/day, and prednisone 30 mg/day. The

Table 1. Clinical course of uveitis and extraocular manifestations of Behçet's disease in patients with Behçet's disease before and during infliximab therapy

			Before infliximab therapy								During infliximab therapy			
Patient no.	Sex	Age (years)	Therapy given to patients before infliximab (listed consecutively)	Uveitis relapse/ month	Mean daily steroid dose (mg prednisone)	Extraocular lesions (number and type) on previous therapy	Follow-up (months)	VA before IFX initiation	Uveitis relapse/month on infliximab	Mean daily steroid dose (mg/prednisone)	Extraocular lesions (number and type) on infliximab	Immunosuppressive treatment administered concomitantly	VA at last examination on infliximab	Follow-up (months)
1	M	29	CyA, IFN, CHL, CyA + Colch	0.5	26.95	1 (arthralgia)	2	RE: 0.8 LE: 0.8	0.5	20	1 (arthralgia)	–	RE: 0.8 LE: 0.8	2[a]
2	F	25	CyA, CyA + AZA, AZA + MTX, IFN	0.5	21.78	2 (oral ulcers)	30	RE: 0.2 LE: 1	0	0.805	0	MTX 15 mg/week	RE: 0.2 LE: 1	30
3	F	36	CyA, MTX, AZA (+NSAIDs)	0.18	0	12 (arthralgia)	22	RE: 1 LE: 1	0	0	8 (arthralgia)	–	RE: 1 LE: 1	22
4	M	28	CyA, IFN	0.23	2.569	3 (hydrarto)	13	RE: 1 LE: 1	0	0	0	–	RE: 1 LE: 1	13
5	M	31	CyA, CyA + AZA, IFN, AZA + MTX	0.392	30.8	2 (oral ulcers)	28	RE: 0.1 LE: 1	0.07	5.45	0	MTX 15 mg/week	RE: 0.2 LE: 1	28
6	M	34	CyA	0.666	23.2876	0	12	RE: 1 LE: 0.1	0.333	17.2	0	–	RE: 1 LE: 0.1	12
7	F	45	CyA, CyA + AZA, AZA + MTX, AZA	0.277	31.4	2 (oral ulcers) 1 (arthralgia)	18	RE: 0.2 LE: 1	0.111	10.98	2 (oral ulcers) 1 (arthralgia)	AZA 50 mg/day	RE: 0.2 LE: 1	18[b]
8	M	38	AZA	0.333	16.08	5 (oral ulcers) 3 (arthralgia)	14	RE: 1 LE: 1	0	6.44	1 (erythema nodosum) 1 (oral ulcers) 1 (arthralgia)	AZA 50 mg/day	RE: 1 LE: 1	14
9	M	34	CyA, MTX	0.16	23.53	0	12	RE: 0.9 LE: 1	0	5.958	0	–	RE: 1 LE: 1	12
10	M	32	CyA, CyA + Colch	0.1	22.0875	2 (oral ulcers)	20	RE: 0.4 LE: 0.9	0.05	12.93	0	–	RE: 0.6 LE: 0.9	20
11	M	42	CyA, AZA	0.46	22.089	0	13	RE: 1 LE: lp	0.3076	3.14	1 (folliculitis)	AZA 50 mg/day	RE: 1 LE: l.p.	13
12	M	40	CyA, CHL	0.375	47.07	1 (oral ulcers)	16	RE: 0.1 LE: 0.1	0.125	15.74	1 (oral ulcers) 1 (arthralgia)	AZA 50 mg/day	RE: 0.1 LE: 0.1	16

Mean number of relapses/month on previous therapy: 0.35 ± 0.17.
Mean number of relapses/month on infliximab therapy: 0.12 ± 0.17, $t = 5.647$, $P < 0.001$.
Mean daily dose of prednisone on previous therapy (11 patients): 24.33 ± 10.84 mg.
Mean daily dose of prednisone on infliximab (11 patients): 8.97 ± 6.81 mg, $t = 5.623$, $P < 0.001$.
Mean number of extraocular lesion on previous therapy: 2.83 ± 3.61.
Mean number of extraocular lesion on infliximab: 1.50 ± 2.35, $t = 2.345$, $P = 0.039$.

VA, visual acuity; RE, right eye; LE, left eye; CyA, cyclosporine A; IFN, interferon α; CHL, chlorambucil; Colch, colchicine; AZA, azathioprine; MTX, methotrexate; IFX, infliximab; NSAID, nonsteroidal anti-inflammatory drug.

[a]Patient 1 stopped infliximab because of the onset of pulmonary tuberculosis.

[b]Patient 7 stopped infliximab because of headaches.

patient was treated successfully with isoniazid 300 mg/day, ethambutol 1200 mg/day, piraldine 1500 mg/day, and rifampicin 600 mg/day, with complete resolution of his pulmonary lesions. Further immunosuppressive therapy was avoided because of the patient's refusal to take antituberculosis chemoprophylaxis for 6 months after computed tomographic documentation of the complete resolution of the pulmonary lesions.

In the 11 patients taking corticosteroids continuously before starting infliximab, the mean daily dose of corticosteroids was reduced from 24.33 ± 10.84 to 8.97 ± 6.81 mg/prednisone per day ($t = 5.623$, $P < 0.001$).

Patient 3, who had displayed anterior uveitis and diffuse necrotizing scleritis, showed a resolution of the scleritis with scleromalacia after the third infusion of infliximab. Previous immunosuppressive therapy was suspended for six patients after infliximab initiation, while the other patients were treated simultaneously with methotrexate 15 mg/week (patients 2 and 5) or azathioprine 50 mg/day (patients 7, 8, 11, and 12).

While the patients were on infliximab therapy, visual acuity remained unchanged in 21 of the 24 eyes studied (87.50%) and improved in three eyes (12.50%).

Patient 1 stopped taking infliximab because of pulmonary tuberculosis. During the 2 months of follow-up after infliximab cessation, he developed one ocular relapse, and the mean daily dose of prednisone was increased from 20 to 27.51 mg/day. Patient 4 was lost to follow-up after 13 months of therapy, and patient 8 decided to suspend the therapy 14 months after infliximab initiation. Patient 7 wanted to stop therapy after 18 months because of headache, although both neurologic examination and nuclear magnetic resonance results were negative, and the headache seemed to be unrelated to the therapy. In the 8 months of additional follow-up, this patient presented with 0.50 relapse/month, while during the treatment she had presented with 0.11 relapse/month. The mean daily dose of steroids had been increased from 10.98 mg/day of prednisone during infliximab therapy to 19.90 mg/day of prednisone after stopping infliximab, although the headache persisted and neurologic examination and nuclear magnetic resonance continued to show negative results.

Eight patients are still on treatment with infliximab (mean treatment duration, 19.12 ± 7.12 months; median, 18 months), and three of the eight have been relapse-free since starting the therapy.

Before infliximab administration, all of the patients had presented with a mean number of BD extraocular lesions (oral ulcers, arthralgia, erythema nodosum, hydrarthrosis) of 2.83 ± 3.61, while during treatment the mean occurrence of extraocular symptoms was 1.50 ± 2.35 ($t = 2.345$, $P = 0.039$). BD-related extraocular manifestations before and during infliximab treatment are reported in Table 1.

Side effects were observed in four patients (33.33%). One developed pulmonary tuberculosis (8.33%); one, herpetic keratitis and a subsequent episode of otitis; one, severe nonocular herpetic infection; and the last, recurrent urinary infections. It is of note that in two of these patients who developed side effects presumably related to infliximab administration, subsequent infliximab infusions were delayed, and during this period the patients showed an ocular relapse (15 and 18 days after the scheduled time for infusion).

C-reactive protein was checked every 3 months and remained at normal levels in all patients throughout the follow-up. No patient developed autoantibodies (nucleus, dsDNA, or antineutrophil cytoplasmic), any autoimmune disease, or thromboembolic events throughout the follow-up.

Discussion

Behçet's disease is a potentially sight-threatening condition and is considered one of the ocular diseases in which immunosuppressive therapy is necessary to preserve visual acuity.[2,3] Standard immunosuppressive agents, such as chlorambucil, cyclophosphamide, and azathioprine, as well as new more recently introduced immunomodulator agents, such as cyclosporine A and interferon α, have proven effective in the treatment of the ocular manifestations of BD.[2,3,25–30] Nevertheless some cases become unresponsive to those treatments, or the onset of side effects compels reduction of the doses or withdrawal from the therapy. Recently, infliximab, an anti-TNFα monoclonal antibody, has proven effective in the treatment of some cases of Behçet's disease[9–19] as well as of refractory uveitis and scleritis.[31]

Three studies on larger numbers of patients have been carried out. Sfikakis and colleagues[16] demonstrated the efficacy of infliximab as a single infusion in 25 patients with BD, achieving a complete resolution of vitreitis and retinitis 28 days after the infusion and a resolution of the cystoid macular edema in 90% of the cases; a complete remission of the disease was observed in 60% of the 15 patients who received additional infliximab infusion. Ohno et al.[15] reported that 13 patients treated with infliximab 5 or 10 mg/kg showed a significant decrease in the mean frequency of ocular attacks and a reduction in the occurrence of extraocular manifestations of BD. All of the patients in this study developed infliximab-related side effects, mainly infections (53%); one patient (7.89%) developed pulmonary tuberculosis.[15] In an open-label trial carried out in Turkey by Tugal-Tutkun et al.[17] on 13 patients, statistically significant reductions in uveitis recurrences, the mean daily dose of prednisolone administered, and the occurrence of oral ulcers were observed. Nevertheless, during the infusion period only four patients remained attack-free (30.7%), and during the entire follow-up period (54 weeks, 21 weeks after infliximab cessation), only one patient did not show any ocular relapse.[17]

We also found in our patients a satisfactory control of the ocular manifestations of BD, achieving a significant reduction in the mean number of ocular relapses in 91.6% of patients ($P < 0.001$). The only patient who did not show a difference in the ocular relapse per month rate between before and after infliximab therapy was treated for only

2 months (three infusions) because of the occurrence of pulmonary tuberculosis.

Infliximab therapy made it possible for us to reduce the mean daily steroid dose administered to our patients, compared with the dosages taken during previous standard immunosuppressive treatments ($P < 0.001$). In this cumulative dose, we included the steroids administered for both ocular and extraocular manifestations, because it is usually impossible to differentiate in a patient with two given localizations of BD reactivation the amount of steroids needed to treat just one of the two manifestations.

Visual acuity remained stable in 87.5% of the eyes and increased in 12.5%, thus confirming good control of the ocular inflammation, although the limited follow-up and number of patients make it difficult to reach definite conclusions. The extraocular manifestations of BD were also significantly reduced by infliximab therapy ($P = 0.039$), as reported also by other authors.[9,13,17,32,33]

Infliximab has been proven effective in the treatment of rheumatoid arthritis and Crohn's disease.[20–22] In patients with such diseases, infliximab has reduced C-reactive protein and proinflammatory cytokines such as interleukin-6 and TNFα.[34] Santos Lacomba et al.[7] demonstrated that TNFα participates actively in the pathogenesis of clinical uveitis, and recently Perez-Guijo et al.[35] have reported an increased concentration of TNFα in the aqueous humor of patients with HLAB27-associated uveitis.

Nevertheless, a recent review on the safety of TNFα has shown that patients treated with TNFα antagonist are subject to an increased risk of serious infections compared with the general population, but the rate was similar to that in rheumatoid arthritis patients treated with other disease-modifying agents. In particular, reactivation of latent tuberculosis can occur.[36–38] In our patient who developed tuberculosis, chest X-ray and PPD skin testing were both negative before infliximab administration. It is well known that rheumatoid arthritis decreases the PPD response,[38] but this decrease may also be due to the administration of several immunosuppressive agents given to the patient in combination with high doses of systemic steroids. In conclusion, no definite conclusion can be drawn as to whether the tuberculosis developed by our patient should be considered a new infection or reactivation of a latent infection.

A question has also been raised about maintenance therapy with infliximab for BD-affected patients. In our experience, only the patient who wanted to stop therapy and another who was compelled to do so because of tuberculosis presented in the posttreatment period a course of disease similar to or worse than that reported during infliximab therapy, in terms of the number of relapses and the mean daily dose of steroids. Furthermore, we also observed that in two patients who delayed the schedule of infliximab infusion because of the occurrence of side effects (infections), a uveitis relapse occurred after a mean time of 16.5 days. These observations, as well as those reported by other authors,[17] may strengthen the hypothesis that maintenance therapy with anti-TNFα agents is warranted in patients with BD after the induction phase of therapy in order to achieve prolonged control of the disease. Further multicenter studies are necessary to fully elucidate the best treatment regimen, possibly pulse therapy in cases of relapsing or chronic BD, and the duration of maintenance therapy with infliximab for patients with Behçet's disease.

Infliximab seems to be a useful alternative therapy for patients with sight-threatening uveitis unresponsive to the standard immunosuppressive therapy. A long-term follow-up of these patients and the experience drawn from the treatment of patients with other similar autoimmune diseases may clarify the real toxicity of infliximab and, eventually, determine its possible use as a first-line treatment for Behçet's disease.

References

1. Behçet H. Über rezidivierende Aphthose, durch ein Virus verursachte Geschwüre in Mund, am Auge und an den Genitalien. Dematol Wochenschr 1937;105:1152, 1157.
2. Pivetti-Pezzi P, Gasparri V, De Liso P, Catarinelli G. Prognosis in Behçet's disease. Ann Ophthalmol 1985;17:20–25.
3. Whitcup SM, Salvo EC Jr, Nussenblatt RB. Combined cyclosporine and corticosteroid therapy for sight-threatening uveitis in Behçet's disease. Am J Ophthalmol 1994;118:39–45.
4. Kaklamani VG, Vaiopoulos G, Kaklamanis PG. Behçet's disease. Semin Arthritis Rheum 1998;27:197–217.
5. Boyd SR, Young S, Lightman S. Immunopathology of the noninfectious posterior and intermediate uveitis. Surv Ophthalmol 2001;46:209–233.
6. Turan B, Gallati H, Erdi H, Gurler A, Michel BA, Viligger PM. Systemic levels of the T cell regulatory cytokines IL-10 and IL-12 in Behçet's disease: soluble TNFR-75 as a biological marker of disease activity. J Rheumatol 1997;24:128–132.
7. Santos Lacomba M, Marcos Martin C, Gallardo Gallera JM, et al. Aqueous humor and serum tumor necrosis factor-alpha in clinical uveitis. Ophthalmic Res 2001;33:251–255.
8. Chronopoulou H, Tzavara V, Oikonomopoulos N, et al. High levels of TNF-α in the aqueous humor in patients suffering from Adamantiades-Behçet's disease: preliminary results. Invest Ophthalmol Vis Sci 2001;42 Suppl 4:S708.
9. Sfikakis PP, Theodossiadis PG, Katsiari CG, Kaklamanis P, Markomichleakis NN. Effect of infliximab on sight-threatening panuveitis in Behçet's disease. Lancet 2001;358:295–296.
10. Munoz-Fernandez S, Hidalgo V, Fernandez-Melon J, Schlinker J, Martin-Mola. Effect of infliximab on threatening panuveitis in Behçet's disease. Lancet 2001;358:1644.
11. Sfikakis PP. Behçet's disease: a new target for anti-tumor necrosis factor treatment. Ann Rheum Dis 2002;61 Suppl II:ii51–ii53.
12. Triolo G, Vadalà M, Accardo-Palumbo A, et al. Anti-tumor necrosis factor monoclonal antibody treatment for ocular Behçet's disease. Ann Rheum Dis 2002;61:560–561.
13. Andreu M, Ramanoelina J, Fajnkuchen F, et al. Traitment de la maladie de Behçet sèvére par un anti-TNFα: l'infliximab. Ann Med Interne 2002;153:414–415.
14. Joseph A, Raj D, Dua HS, Powell PT, Lanyon PC, Powell RJ. Infliximab in the treatment of refractory posterior uveitis. Ophthalmology 2003;110:1449–1453.
15. Ohno S, Nakamura S, Hori S, et al. Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. J Rheumatol 2004;31:1362–1368.
16. Sfikakis PP, Kaklamanis PH, Elezoglou A, et al. Infliximab for recurrent, sight-threatening ocular inflammation in Adamantiades-Behçet's disease. Ann Intern Med 2004;140:404–406.

17. Tugal-Tutkun I, Mudun A, Urgancioglu M, et al. Efficacy of infliximab in the treatment of uveitis that is resistant to treatment with the combination of azathioprine, cyclosporine, and corticosteroids in Behçet's disease. An open-label trial. Arthritis Rheum 2005;52:2478–2484.
18. Benitez-del-Castillo JM, Martinez-de-la-Casa JM, Pato-Cotor E, et al. Long-term treatment of refractory posterior uveitis with anti-TNF α (infliximab). Eye 2005;19:841–845.
19. Lindsted EW, Baarsma GS, Kuijpers RWAM, van Hagen PM. Anti-TNFα therapy for sight-threatening uveitis. Br J Ophthalmol 2005;89:533–536.
20. Elliott MJ, Maini RM, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor alpha (cA2) versus placebo in rheumatoid arthritis. Lancet 1994;344:1105–1110.
21. Lipsky PE, van der Heijde DMF, St Claire EW, et al. Anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study group. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594–1602.
22. Targan SR, Hanauer SB, van Deventer SJ, et al. Crohn's disease cA2 Study Group. A short term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. N Engl J Med 1997;337:1029–1035.
23. Scallon B, Cai A, Solowski N, et al. Binding and functional comparison of two types of tumor necrosis factor (TNF) antagonist. J Pharmacol Exp Ther 2002;301:418–426.
24. International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's Disease. Lancet 1990;335:1078–1080.
25. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporine versus colchicine and long-term open study of cyclosporine in Behçet's disease. Lancet 1989;1:1093–1096.
26. Hamuryudan V, Ozyazgan Y, Hizli N, et al. Azathioprine in Behçet's syndrome: effects on long-term prognosis. Arthritis Rheum 1997;40:769–774.
27. Pivetti-Pezzi P, Accorinti M, Pirraglia MP, Priori R. Valesini G. Interferon alpha for ocular Behçet's disease. Acta Ophthalmologica Scand 1997;75:720–722.
28. Okada AA. Drug therapy in Behçet's disease. Ocul Immunol Inflamm 2000;130:774–781.
29. Goldstein DA, Fontanilla FA, Kaul S, Sain O, Tessler HH. Long-term follow-up of patients treated with short-term high-dose chlorambucil for sight-threatening ocular inflammation. Ophthalmology 2002;109:370–377.
30. Kotter I, Zierhut M, Eckstein AK, et al. Human recombinant interferon alpha 2a for the treatment of Behçet's disease with sight-threatening posterior or panuveitis. Br J Ophthalmol 2003;87:423–431.
31. Murphy CC, Ayliffe WH, Booth A, Makanjula D, Andrews PA, Jayne D. Tumor necrosis factor alpha blockade with infliximab for refractory uveitis and scleritis. Ophthalmology 2004;111:352–356.
32. Saulsbury FT, Mann JA. Treatment with infliximab for a child with Behçet's disease. Arthritis Rheum 2003;49:599–600.
33. Licata G, Pinto A, Tuttolomondo A, et al. Anti-tumor necrosis factor a monoclonal antibody therapy for recalcitrant cerebral vasculitis in a patient with Behçet's syndrome. Ann Rheum Dis 2003;62:280–281.
34. Charles P, Elliott MJ, Davis D, et al. Regulation of cytokines, cytokine inhibitors, and acute phase proteins following anti-TNF-alpha therapy in rheumatoid arthritis. J Immunol 1999;163:1521–1528.
35. Perez-Guijo V, Santos-Lacomba M, Sanchez-Hernandez M, et al. Tumor necrosis factor-alpha levels in aqueous humor and serum from patients with uveitis: the involvement of HLA-B27. Curr Med Res Opin 2004;20:155–157.
36. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor-necrosis factor alpha-neutralizing agent. N Engl J Med 2001;345:1098–1104.
37. Lim WS, Powell RJ, Johnston ID. Tuberculosis and treatment with infliximab. N Engl J Med 2002;346:623–626.
38. Khanna D, McMahon M, Furst DE. Safety of tumor necrosis factor-α antagonists. Drug Safety 2004;27:307–324.