HOKKAIDO UNIVERSITY

Title	Correlation between elevation of serum antinuclear antibody titer and decreased therapeutic efficacy in the treatment of Behçet's disease with infliximab
Author(s)	Iwata, Daiju; Namba, Kenichi; Mizuuchi, Kazuomi et al.
Citation	Graefe's Archive for Clinical and Experimental Ophthalmology, 250(7), 1081-1087 https://doi.org/10.1007/s00417-011-1908-1
Issue Date	2012-07
Doc URL	https://hdl.handle.net/2115/52973
Rights	The original publication is available at www.springerlink.com
Type	journal article
File Information	GACE0250-7_1081-1087.pdf



Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Correlation between elevation of serum antinuclear antibody titre and decreased therapeutic efficacy in the treatment of Behçet's disease with infliximab.

Daiju Iwata[1], Kenichi Namba[1], Kazuomi Mizuuchi[1], Nobuyoshi Kitaichi[2,3], Satoru Kase[1,], Yuko Takemoto[1], Shigeaki Ohno[3], Susumu Ishida[1]

1. Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

2. Department of Ophthalmology, Health Sciences University of Hokkaido, Sapporo, Japan

3. Department of Ocular Inflammation and Immunology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence to: Kenichi Namba MD, PhD

Department of Ophthalmology, Hokkaido University Graduate School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan

E-mail: knamba@med.hokudai.ac.jp

Abstract

Background: Infliximab, an anti-TNF-α monoclonal antibody, administered to Behçet's disease (BD) patients in Japan with refractory intraocular inflammation has shown excellent clinical results. However, some patients demonstrate a decreased response to infliximab during the course of the treatment. In the present study, we investigated the correlation between this reduced therapeutic effect and elevation of the serum antinuclear antibody (ANA) titres in patients with BD who were undergoing infliximab therapy.

Methods: Seventeen patients (14 males and 3 females) with uveitis in BD who were undergoing treatment with infliximab for 2 years or longer were enrolled. Their blood test results and clinical histories were obtained from medical records.

Results: One patient (5.9%) was ANA-positive prior to the initiation of infliximab, and 11 patients (64.7％) developed positive ANA during the therapy. The appearance of ANA was observed 6 months after the initiation of the infliximab therapy, and its titres gradually increased. None of the patients showed lupus symptoms. Five patients (29.4％) have suffered from ocular inflammatory attacks since 6th month from the initiation of infliximab treatment and all of them were ANA-positive. In contrast, 4 patients (23.5%) who were ANA-negative experienced no ocular attacks during the follow-up period.

Conclusions: Here we report the positive conversion and subsequent elevation of serum ANA titres in some patients with BD after the initiation of infliximab therapy. Since all recurrences of uveitis were shown only in the ANA positive patients, serum ANA titre may be a helpful biomarker for predicting the recurrence of ocular attacks in BD patients treated with anti-TNF-α antibody therapies.

Key words: Behçet’s disease, retinal vasculitis, uveitis, antinuclear antibody, Infliximab, biomarker, anti-TNF-a monoclonal antibody

Introduction

Behçet's disease (BD) is a chronic systemic inflammatory disease characterized by recurrent oral aphthous ulcers, genital ulcers, skin lesions, gastrointestinal involvement, vasculitis, neurological manifestations and intraocular inflammation. BD is one of the major aetiologies of endogenous uveitis in Japan[1]; however, its prevalence and clinical features vary among countries and ethnic groups[2, 3]. Recurrent episodes of inflammatory ocular attacks can cause severe visual loss. To prevent the relapse of intraocular inflammation, colchicine and various immunosuppressive agents are administered including cyclosporine A (CyA), which is a selective immunosuppressive agent of T-lymphocytes. However, some patients cannot use these drugs due to intolerable side effects. Moreover, some patient's diseases are refractory to these agents and can progress to vision loss[4-6].

Infliximab (IFX) is a chimeric monoclonal antibody to TNF-α that can minimize the immunological response when used in humans[7]. It neutralizes both membrane-binding and soluble TNF-α, in addition to suppressing TNF-α production by macrophages. IFX is commonly administered to patients with rheumatoid arthritis[8, 9], Crohn's disease[10], psoriasis[11, 12] and in case of refractory uveitis with non-infectious aetiologies including BD[13-20]. IFX is effective for preventing relapse of intraocular inflammations in BD and its efficacy has been well documented in previous studies[13-19]. In Japan, IFX was approved for use in BD patients with refractory uveoretinitis by the Ministry of Health, Labour and Welfare, Japan in January 2007 based on the excellent results from multicentre clinical trials[15, 21]. Though IFX is an excellent agent in the treatment of the BD with refractory uveoretinitis, it has been observed to have decreased efficacy in a subset of BD patients with uveoretinitis[19]. One report showed the development of autoantibodies including antinuclear antibody (ANA) during IFX treatment in BD[22], however, the mechanisms and the meanings of it remain unknown.

In the present study, we investigated ANA titres of the BD patients receiving IFX therapy and examined the correlation between the elevation of ANA and the therapeutic efficacy.

Material and Methods

BD patients with refractory uveoretinitis who had been administered IFX for 2 years or longer were enrolled at Hokkaido University Hospital. The results of their blood tests and clinical histories were obtained from medical records. BD was diagnosed based on the criteria set by the BD Research Committee of Japan, which is part of the Ministry of Health, Labour and Welfare, Japan[23]. The level of ocular inflammation was graded by means of the Standardization of Uveitis Nomenclature (SUN) grading criteria[24]. When a patient showed more than 2 step increase in level of inflammation or increase from grade 3+ to 4+, it was considered an inflammatory ocular attack. Ocular attacks of BD flare up repeatedly and usually disappear within a few weeks. Each ocular attack shows varying degree of uveitis including only mild iridocyclitis or severe obstructive retinal vasculitis with retinal exudates. Number of ocular attacks was counted regardless of the severity and added both eyes.

Patients were administered 5 mg/kg of IFX intravenously at weeks 0, 2, 6 as the initial series of infusions, and thereafter, every 8 weeks. Serum ANA and anti-double-stranded DNA (dsDNA) antibodies were examined prior to IFX infusion. ANA titres were quantified using an indirect immunofluorescence technique using human epithelial (Hep2) cells. Results were classified as positive (ANA $\geq$ 80) or negative (ANA $\leq$ 40) according to previous reports[25-31]. Anti-dsDNA antibodies were identified using enzyme-linked immunosorbent assay (ELISA).

Statistical analyses were performed using the Mann-Whitney U test; p values <0.05 were considered to be

statistically significant.

This study followed the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of Hokkaido University Hospital.

Results

The demographics and clinical characteristics of the 17 Japanese patients, i.e. 14 (82.4%) males and 3 (17.6%) females ranging in age from 15 to 58 (mean age: 36.9) years, enrolled in the study are listed in Table 1. The rate of ocular inflammatory attacks during 6 months prior to the initiation of IFX was 3.8 ± 2.1 (mean ± SD). IFX therapy significantly reduced the rate of ocular attacks to 0.7 ± 1.1 during the first 6 months after the initiation of IFX ($P < 0.01$). 8 patients (47.1%) achieved no relapse of ocular inflammatory attacks between the first infusion and the 24-month visit. Five patients (29.4%) experienced only one ocular inflammatory attack and four patients (23.5%) experienced several ocular attacks during the follow-up period. It was not necessary to administer concomitant drugs with IFX for 12 patients. Three of five patients who were previously administered oral prednisolone (PSL) could decrease and gradually stop their therapy after IFX initiation. Two of these patients required continued PSL administration to control neurological symptoms.

Best-corrected visual acuities (BCVA) were reported 1 year after the initiation of IFX; IFX therapy had successfully maintained their vision acuity (Figure 1).

ANA profiles and the frequency of ocular attacks in BD patients treated with IFX are shown in Table 2. One patient (5.9%) was ANA-positive prior to the initiation of IFX. Anti-dsDNA antibodies were never detected prior to IFX induction. The change in ANA-positive rates is shown in Figure 2. The positive conversion of ANA

became common 6 months after the initiation of IFX, and the positive titres continued to increase. At the end of the follow-up period, 13 patients (76.4%) were identified positive for ANA (Figure 2). One patient (5.9%) developed anti-dsDNA antibodies (case #14). However, no patient showed lupus symptoms.

The correlation of ocular attacks with elevation of ANA titre is shown in Figure 3. At 6th month after the IFX induction, 5 patients (29.4%) were ANA-positive and 12 (70.6%) were negative. In the ANA-positive group, 3 patients (60%) had ocular inflammatory attacks during the first 6 months after IFX administrations, whereas in the ANA-negative group, 4 (33.3%) patients had these attacks. Ocular attacks were much milder than those before IFX therapy both in the ANA-negative group and ANA-positive group.

However, since the 6th month of IFX therapy, all of 5 patients (29.4%) suffering from a relapse of ocular inflammatory attacks was ANA-positive. And, 3 of 5 patients had multiple ocular attacks. In the 2 of these 3 patients, administration interval was shortened from 8 to 7 weeks, and it successfully led to less rate of the ocular attacks again. On the other hand, all of 4 patients (23.5%) with negative ANA had no ocular attacks.

Discussion

ANA appeared in the sera of BD patients 6 months after IFX induction, and its titre gradually increased. It was reported that development of ANA and anti-dsDNA antibodies is seen during the course of anti-TNF-α therapy in patients with some autoimmune diseases such as rheumatoid arthritis[32-34], psoriasis[35], Crohn's disease[36], and BD[22]. In the present study, 75.0% of the patients converted to ANA-positive during the course of IFX therapy and positive ANA titres (1: 80) had been detected in one patient on study enrolment. This patient experienced 2- fold increase in the titre (1:160). Only one patient (5.9%) converted to anti-dsDNA antibody

positive during the follow-up period. These findings are consistent with previous studies of other autoimmune rheumatoid diseases, which reported that 25–71% and 4–46% patients became positive for ANA and anti-dsDNA antibodies after IFX initiation in case of psoriasis and rheumatoid arthritis[32, 37, 38]. In these previous studies, a small number of patients had lupus-like symptoms[39-41]. Suhler EB et al also reported the results of a prospective study in which 23 patients with non-infectious uveoretinitis including 4 of BD patients were enrolled[42]. In the report, ANA titres developed in 15 (75.0%) of the 20 patients and 2 patients with very high titre showed arthritis. Although any patient has not showed lupus symptoms in our study, we have to observe patients very carefully.

It is still unknown how ANA and anti-dsDNA antibodies develop during IFX therapy. One possible explanation is that TNF-α may up-regulate cellular expression of the adhesion molecule CD44, which plays a role in the clearance of apoptotic neutrophils by phagocytes[43, 44]. Impaired clearance of apoptotic cells and reduced CD44 expression on leukocytes has been reported in systemic lupus erythematosus (SLE)[45, 46]. IFX may down-regulate CD44 expression and induce an immune reaction toward their own nuclei by impairment of the clearance of apoptotic cells.

In the present study, we also demonstrated the association between the development of ANA and reduced effects of IFX therapy in BD patients. Only a few studies reported the association of serum ANA development with the effects of IFX [35, 42]. Pink AE et al reported that ANA titre was associated with the loss of response to anti-TNF-α therapy in psoriasis. In our study, during 6 months after the initiation of IFX therapy, several patients experienced mild ocular inflammatory attacks, both in the ANA-positive and ANA-negative groups. Presumably, it takes some time for IFX to exert an inhibitory effect on severe ocular inflammation in BD patients.

However, after the 6th month IFX therapy, the cases suffering from the relapse of ocular inflammatory attacks were limited to ANA-positive patients. Similar to the study in psoriasis[35], these results suggest that the development of elevated levels of serum ANA may be associated with the reduction of IFX efficacy for BD patients. Suhler EB et al mentioned no clear relation between the development of ANAs and ocular therapeutic response [42]. The subjects in the report included variety of uveitis, in contrast to our study targeted only on BD. The tight disease enrollment may be the reason why we could show the relation between recurrences of uveitis and high titre of ANA.

The exact association between ANA and IFX also remain unknown. It has also been found that repeated infusion of IFX leads to induction of antibodies to IFX (ATI) that reduce the efficacy of IFX. This phenomenon has been a serious issue in rheumatoid arthritis[47], Crohn's disease[48], psoriasis [49, 50] and BD[51] therapy. ANA and ATI, both of which appear during the course of IFX treatment are likely to be involved in the reduced efficacy of IFX; however, the correlation between the two antibodies remains to be elucidated. We speculate that repeated administration of protein agents such as IFX may activate a systemic immune response, leading to the production of various autoantibodies including ANA and ATI. Therefore, detection of high titer of ANA indicates the development of ATI in the patients. According to this theory, the patients, such as cases #6 and #7, with high ANA titre (640×) may have already had ATI. These patients should be monitored closely for further symptoms. If this theory is confirmed that ATI is strongly correlated with the decreased therapeutic efficacy of IFX, we need to consider concomitant use of immune modulatory medicine in BD.

IFX has provided a new way to maintain good vision for a long time in many BD patients with severe uveitis. However, while using IFX with long-term, IFX becomes less effective in certain cases. Serum ANA titres may be

one of the helpful biomarker to predict IFX ineffectiveness.

Competing interests: None

Funding: None

Ethics approval: The study was approved by the institutional Ethics Committee of Hokkaido University

Patient consent: Obtained

Figure legends

Figure 1. Visual acuity before and after initiation of IFX

Best-corrected visual acuities (BCVA) 1 year after the initiation of IFX. IFX therapy successfully maintained the visual acuity in these patients.

Figure 2. Frequencies of ANA positivity in BD patients undergoing IFX therapy

The positive conversion of ANA became frequent 6 months after the initiation of IFX, and its positivity rate gradually increased.

Figure 3. Correlation of ocular attacks with elevation of ANA titre

Since the 6^{th} month of IFX therapy, all of 5 patients (23.5%) suffering from a relapse of ocular inflammatory attack was ANA-positive. And, 3 of 5 patients had ocular attacks more than once throughout the observation period.

References

1. Kitamei H, Kitaichi N, Namba K, Kotake S, Goda C, Kitamura M, Miyazaki A, Ohno S (2009) Clinical features of intraocular inflammation in Hokkaido, Japan. Acta Ophthalmol 87: 424-428
2. Kitaichi N, Miyazaki A, Iwata D, Ohno S, Stanford MR, Chams H (2007) Ocular features of Behcet's disease: an international collaborative study. Br J Ophthalmol 91: 1579-1582
3. Kitaichi N, Miyazaki A, Stanford MR, Iwata D, Chams H, Ohno S (2009) Low prevalence of juvenile-onset Behcet's disease with uveitis in East/South Asian people. Br J Ophthalmol 93: 1428-1430
4. Kaklamani V, Vaiopoulos G, Kaklamanis P (1998) Behçet's Disease. Semin Arthritis Rheum 27: 197-217
5. Sakane T, Takeno M, Suzuki N, Inaba G (1999) Behçet's disease. N Engl J Med 341: 1284-1291
6. Zouboulis C (1999) Epidemiology of Adamantiades-Behçet's disease. Ann Med Interne (Paris) 150: 488-498
7. Knight D, Trinh H, Le J, Siegel S, Shealy D, McDonough M, Scallon B, Moore M, Vilcek J, Daddona P (1993) Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 30: 1443-1453
8. Elliott M, Maini R, Feldmann M, Long-Fox A, Charles P, Bijl H, Woody J (1994) Repeated therapy with monoclonal antibody to tumour necrosis factor alpha (cA2) in patients with rheumatoid arthritis. Lancet 344: 1125-1127
9. Maini R, St Clair E, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, Emery P, Harriman G, Feldmann M, Lipsky P (1999) Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 354: 1932-1939
10. Hanauer S, Feagan B, Lichtenstein G, Mayer L, Schreiber S, Colombel J, Rachmilewitz D, Wolf D, Olson A, Bao W, Rutgeerts P, Group AIS (2002) Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 359: 1541-1549
11. Zhang Z, Schmitt J, Wozel G, Kirch W (2009) [Treatment of plaque psoriasis with biologics. A meta-analysis of randomized controlled trials]. Med Klin (Munich) 104: 125-136
12. Nestle F, Kaplan D, Barker J (2009) Psoriasis. N Engl J Med 361: 496-509
13. Sfikakis P, Theodossiadis P, Katsiari C, Kaklamanis P, Markomichelakis N (2001) Effect of infliximab on sight-threatening panuveitis in Behçet's disease. Lancet 358: 295-296
14. Muñoz-Fernández S, Hidalgo V, Fernández-Melón J, Schlincker A, Martín-Mola E (2001) Effect of infliximab on threatening panuveitis in Behçet's disease. Lancet 358: 1644
15. Ohno S, Nakamura S, Hori S, Shimakawa M, Kawashima H, Mochizuki M, Sugita S, Ueno S, Yoshizaki K, Inaba G (2004) Efficacy, safety, and pharmacokinetics of multiple administration of infliximab in Behçet's disease with refractory uveoretinitis. J Rheumatol 31: 1362-1368

16. Sfikakis P, Kaklamanis P, Elezoglou A, Katsilambros N, Theodossiadis P, Papaefthimiou S, Markomichelakis N (2004) Infliximab for recurrent, sight-threatening ocular inflammation in Adamantiades-Behçet disease. Ann Intern Med 140: 404-406
17. Tugal-Tutkun I, Mudun A, Urgancioglu M, Kamali S, Kasapoglu E, Inanc M, Gül A (2005) 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 52: 2478-2484
18. Accorinti M, Pirraglia M, Paroli M, Priori R, Conti F, Pivetti-Pezzi P (2007) Infliximab treatment for ocular and extraocular manifestations of Behçet's disease. Jpn J Ophthalmol 51: 191-196
19. Niccoli L, Nannini C, Benucci M, Chindamo D, Cassarà E, Salvarani C, Cimino L, Gini G, Lenzetti I, Cantini F (2007) Long-term efficacy of infliximab in refractory posterior uveitis of Behcet's disease: a 24-month follow-up study. Rheumatology (Oxford) 46: 1161-1164
20. Al-Rayes H, Al-Swailem R, Al-Balawi M, Al-Dohayan N, Al-Zaidi S, Tariq M (2008) Safety and efficacy of infliximab therapy in active behcet's uveitis: an open-label trial. Rheumatol Int 29: 53-57
21. Yamada Y, Sugita S, Tanaka H, Kamoi K, Kawaguchi T, Mochizuki M (2010) Comparison of infliximab versus ciclosporin during the initial 6-month treatment period in Behçet disease. Br J Ophthalmol 94: 284-288
22. Elezoglou A, Kafasi N, Kaklamanis PH, Theodossiadis PG, Kapsimali V, Choremi E, Vaiopoulos G, Sfikakis PP (2007) Infliximab treatment-induced formation of autoantibodies is common in Behçet's disease. Clin Exp Rheumatol 25: S65-69
23. Mizushima Y (1988) Recent research into Behçet's disease in Japan. Int J Tissue React 10: 59-65
24. Jabs DA, Nussenblatt RB, Rosenbaum JT, Group SoUNSW (2005) Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 140: 509-516
25. Fritzler MJ, Pauls JD, Kinsella TD, Bowen TJ (1985) Antinuclear, anticytoplasmic, and anti-Sjogren's syndrome antigen A (SS-A/Ro) antibodies in female blood donors. Clin Immunol Immunopathol 36: 120-128
26. de Vlam K, De Keyser F, Verbruggen G, Vandenbossche M, Vanneuville B, D'Haese D, Veys EM (1993) Detection and identification of antinuclear autoantibodies in the serum of normal blood donors. Clin Exp Rheumatol 11: 393-397
27. Forslid J, Heigl Z, Jonsson J, Scheynius A (1994) The prevalence of antinuclear antibodies in healthy young persons and adults, comparing rat liver tissue sections with HEp-2 cells as antigen substrate. Clin Exp Rheumatol 12: 137-141
28. Tan EM, Feltkamp TE, Smolen JS, Butcher B, Dawkins R, Fritzler MJ, Gordon T, Hardin JA, Kalden JR, Lahita RG, Maini RN, McDougal JS, Rothfield NF, Smeenk RJ, Takasaki Y, Wiik A, Wilson MR, Koziol JA (1997) Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum 40: 1601-1611
29. Fernandez SA, Lobo AZ, Oliveira ZN, Fukumori LM, P rigo AM, Rivitti EA (2003) Prevalence of

antinuclear autoantibodies in the serum of normal blood dornors. Rev Hosp Clin Fac Med Sao Paulo 58: 315-319

30. Watanabe A, Kodera M, Sugiura K, Usuda T, Tan EM, Takasaki Y, Tomita Y, Muro Y (2004) Anti-DFS70 antibodies in 597 healthy hospital workers. Arthritis Rheum 50: 892-900
31. Al Jabri AA, Al Buloshi MS (2004) Anticardiolipin and antinuclear antibodies in the adult healthy Omani individuals. Saudi Med J 25: 313-317
32. De Rycke L, Kruithof E, Van Damme N, Hoffman IE, Van den Bossche N, Van den Bosch F, Veys EM, De Keyser F (2003) Antinuclear antibodies following infliximab treatment in patients with rheumatoid arthritis or spondylarthropathy. Arthritis Rheum 48: 1015-1023
33. Elkayam O, Burke M, Vardinon N, Zakut V, Yitzhak RB, Paran D, Levartovsky D, Litinsky I, Caspi D (2005) Autoantibodies profile of rheumatoid arthritis patients during treatment with infliximab. Autoimmunity 38: 155-160
34. Eriksson C, Engstrand S, Sundqvist KG, Rantapää-Dahlqvist S (2005) Autoantibody formation in patients with rheumatoid arthritis treated with anti-TNF alpha. Ann Rheum Dis 64: 403-407
35. Pink AE, Fonia A, Allen MH, Smith CH, Barker JN (2010) Antinuclear antibodies associate with loss of response to antitumour necrosis factor-alpha therapy in psoriasis: a retrospective, observational study. Br J Dermatol 162: 780-785
36. Nancey S, Blanvillain E, Parmentier B, Flourié B, Bayet C, Bienvenu J, Fabien N (2005) Infliximab treatment does not induce organ-specific or nonorgan-specific autoantibodies other than antinuclear and anti-double-stranded DNA autoantibodies in Crohn's disease. Inflamm Bowel Dis 11: 986-991
37. Smith CH, Jackson K, Bashir SJ, Perez A, Chew AL, Powell AM, Wain M, Barker JN (2006) Infliximab for severe, treatment-resistant psoriasis: a prospective, open-label study. Br J Dermatol 155: 160-169
38. Charles PJ, Smeenk RJ, De Jong J, Feldmann M, Maini RN (2000) Assessment of antibodies to double-stranded DNA induced in rheumatoid arthritis patients following treatment with infliximab, a monoclonal antibody to tumor necrosis factor alpha: findings in open-label and randomized placebo-controlled trials. Arthritis Rheum 43: 2383-2390
39. Cairns AP, Duncan MK, Hinder AE, Taggart AJ (2002) New onset systemic lupus erythematosus in a patient receiving etanercept for rheumatoid arthritis. Ann Rheum Dis 61: 1031-1032
40. Debandt M, Vittecoq O, Descamps V, Le Loët X, Meyer O (2003) Anti-TNF-alpha-induced systemic lupus syndrome. Clin Rheumatol 22: 56-61
41. Favalli EG, Sinigaglia L, Varenna M, Arnoldi C (2002) Drug-induced lupus following treatment with infliximab in rheumatoid arthritis. Lupus 11: 753-755
42. Suhler EB, Smith JR, Wertheim MS, Lauer AK, Kurz DE, Pickard TD, Rosenbaum JT (2005) A prospective trial of infliximab therapy for refractory uveitis: preliminary safety and efficacy outcomes. Arch Ophthalmol 123: 903-912
43. Osada A, Nakashima H, Furue M, Tamaki K (1995) Up-regulation of CD44 expression by tumor necrosis factor-alpha is neutralized by interleukin-10 in Langerhans cells. J Invest Dermatol

105: 124-127

44. Hart SP, Dougherty GJ, Haslett C, Dransfield I (1997) CD44 regulates phagocytosis of apoptotic neutrophil granulocytes, but not apoptotic lymphocytes, by human macrophages. J Immunol 159: 919-925
45. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR (1998) Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. Arthritis Rheum 41: 1241-1250
46. Cairns AP, Crockard AD, McConnell JR, Courtney PA, Bell AL (2001) Reduced expression of CD44 on monocytes and neutrophils in systemic lupus erythematosus: relations with apoptotic neutrophils and disease activity. Ann Rheum Dis 60: 950-955
47. Finckh A, Dudler J, Wermelinger F, Ciurea A, Kyburz D, Gabay C, Bas S, SCQM po (2010) Influence of anti-infliximab antibodies and residual infliximab concentrations on the occurrence of acquired drug resistance to infliximab in rheumatoid arthritis patients. Joint Bone Spine 77: 313-318
48. Yamada A, Sono K, Hosoe N, Takada N, Suzuki Y (2010) Monitoring functional serum antitumor necrosis factor antibody level in Crohn's disease patients who maintained and those who lost response to anti-TNF. Inflamm Bowel Dis 16: 1898-1904
49. Reich K, Nestle FO, Papp K, Ortonne JP, Evans R, Guzzo C, Li S, Dooley LT, Griffiths CE, investigators Es (2005) Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. Lancet 366: 1367-1374
50. Adişen E, Aral A, Aybay C, Gürer MA (2010) Anti-infliximab antibody status and its relation to clinical response in psoriatic patients: A pilot study. J Dermatol 37: 708-713
51. Sugita S, Yamada Y, Mochizuki M (2010) Relationship between serum infliximab levels and acute uveitis attacks in patients with Behcet disease. Br J Ophthalmol 95: 549-552

Case	Age (years)	Sex	Treatment before IFX initiation	Concomitant treatment with IFX
1	39	M	CyA, Col, PSL	-
2	33	M	Col, PSL	PSL
3	58	M	Col	-
4	42	M	Col	-
5	40	F	PSL	PSL
6	31	M	Col	-
7	44	M	PSL	PSL
8	54	M	CyA, PSL	PSL
9	17	M	CyA, Col	-
10	52	M	Col	-
11	10	M	-	-
12	49	M	CyA	-
13	40	M	CyA	-
14	40	F	CyA	-
15	36	F	PSL	PSL
16	15	M	PSL	-
17	28	M	-	-

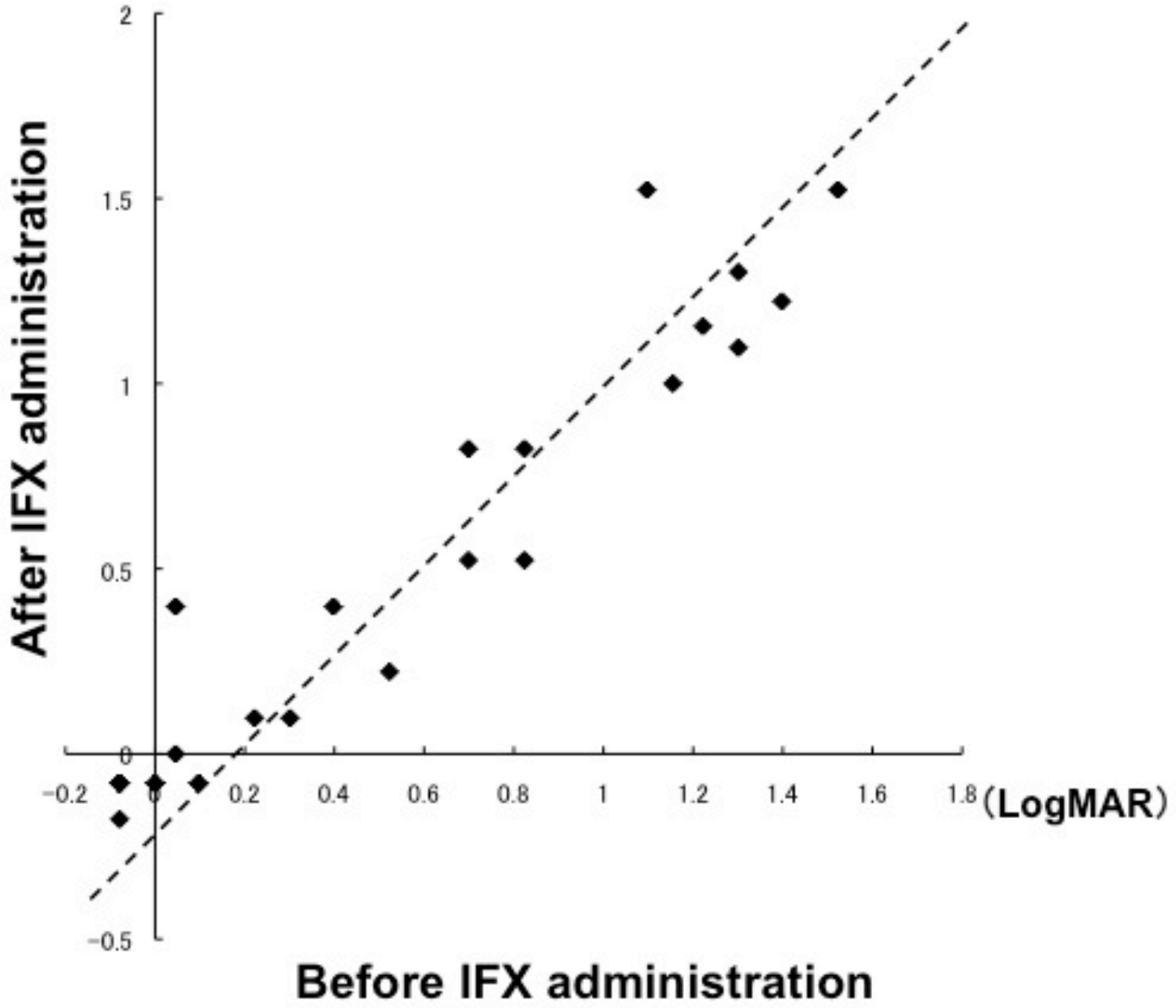
Table 1. Characteristics of Behçet's disease patients treated with IFX

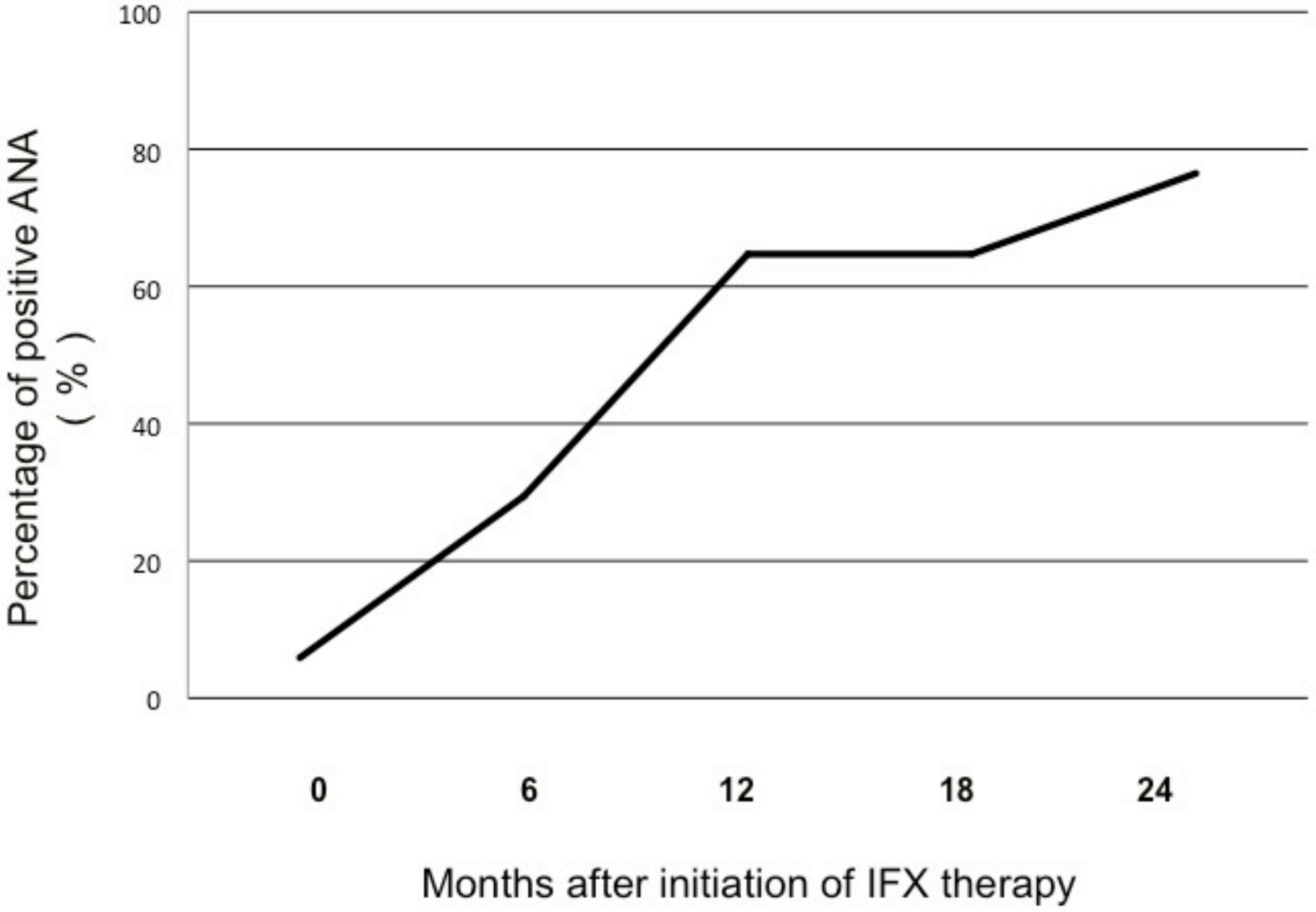
IFX – infliximab, CyA – cyclosporine A, Col – colchicine, PSL – prednisolone

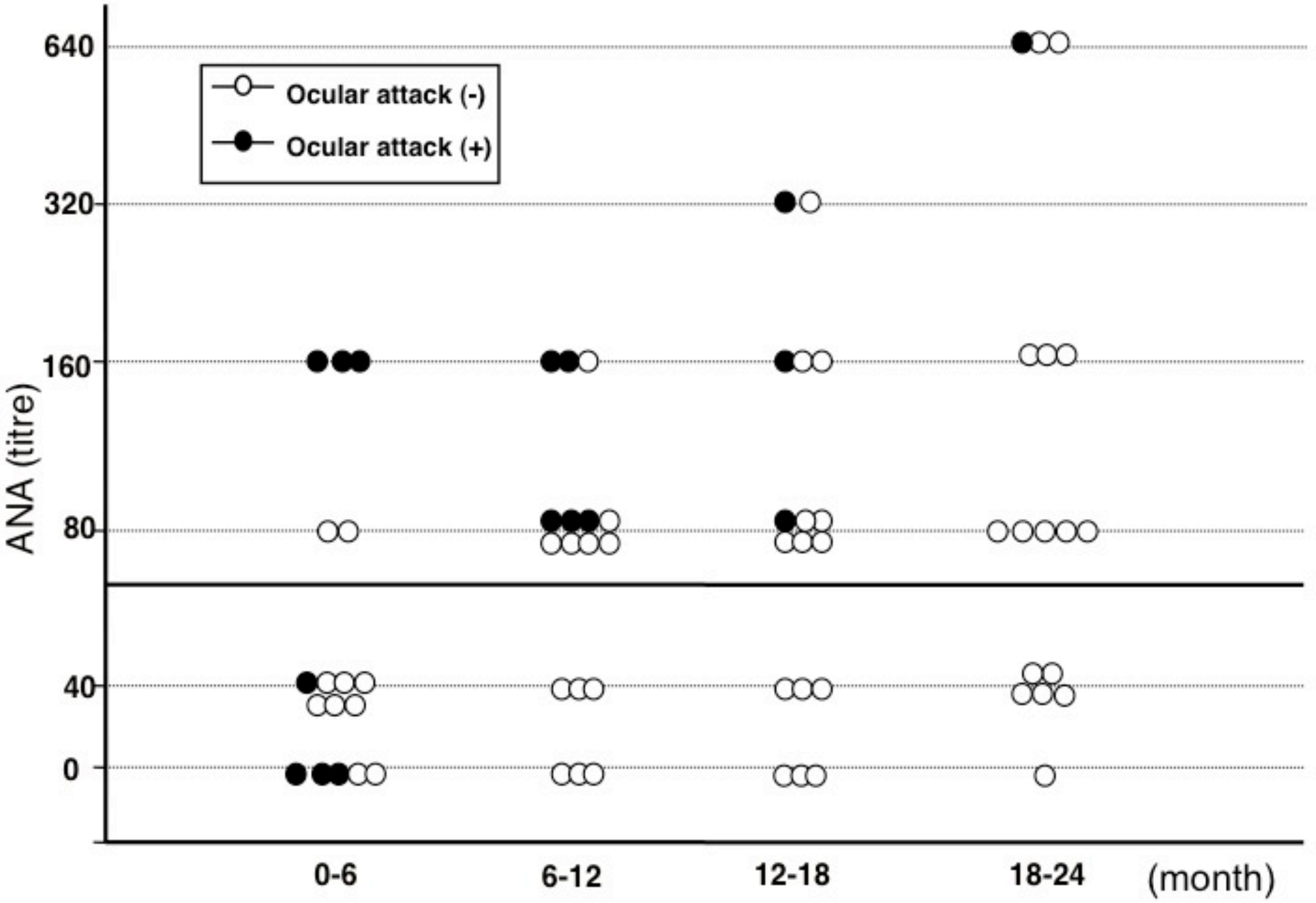
Case	Frequency of ocular attacks -6～0month	ANA (titre) 0month	Frequency of ocular attacks 0～6month	ANA (titre) 6month	Frequency of ocular attacks 6～12month	ANA (titre) 12month	Frequency of ocular attacks 12～18month	ANA (titre) 18month	Frequency of ocular attacks 18～24month	ANA (titre) 24month
1	0	0	0	80	0	40	0	80	0	80
2	2	0	0	0	0	0	0	0	0	40
3	8	0	0	0	0	0	0	0	0	40
4	4	0	0	40	0	80	0	80	0	160
5	4	0	0	40	0	80	0	80	0	160
6	5	0	0	40	0	160	0	320	0	640
7	3	0	0	40	0	80	0	160	0	640
8	1	0	0	40	0	40	0	40	0	40
9	4	0	1	0	0	40	0	40	0	80
10	2	0	1	0	0	80	0	80	0	80
11	4	0	1	0	0	0	0	0	0	0
12	4	40	1	80	0	80	0	80	0	80
13	4	0	0	160	1	80	0	160	0	80
14	7	0	1	160	5	160	4	320	3	640
15	2	0	0	40	1	80	1	80	0	40
16	6	80	2	160	1	160	1	160	0	160
17	4	0	4	40	1	80	0	40	0	40

Table 2. ANA profile and the frequency of ocular attacks of Behçet's disease patients treated with IFX

ANA positive：ANA titer ≥ 80,　ANA – anti nuclear antibody


After IFX administration
2
1.5
1
0.5
0
−0.5
−0.2
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
(LogMAR)
Before IFX administration


100
80
60
40
20
0
Percentage of positive ANA
(%)
0
6
12
18
24
Months after initiation of IFX therapy


640
320
160
80
40
0
ANA (titre)
Ocular attack (-)
Ocular attack (+)
0-6
6-12
12-18
18-24
(month)