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

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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.

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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	-	-

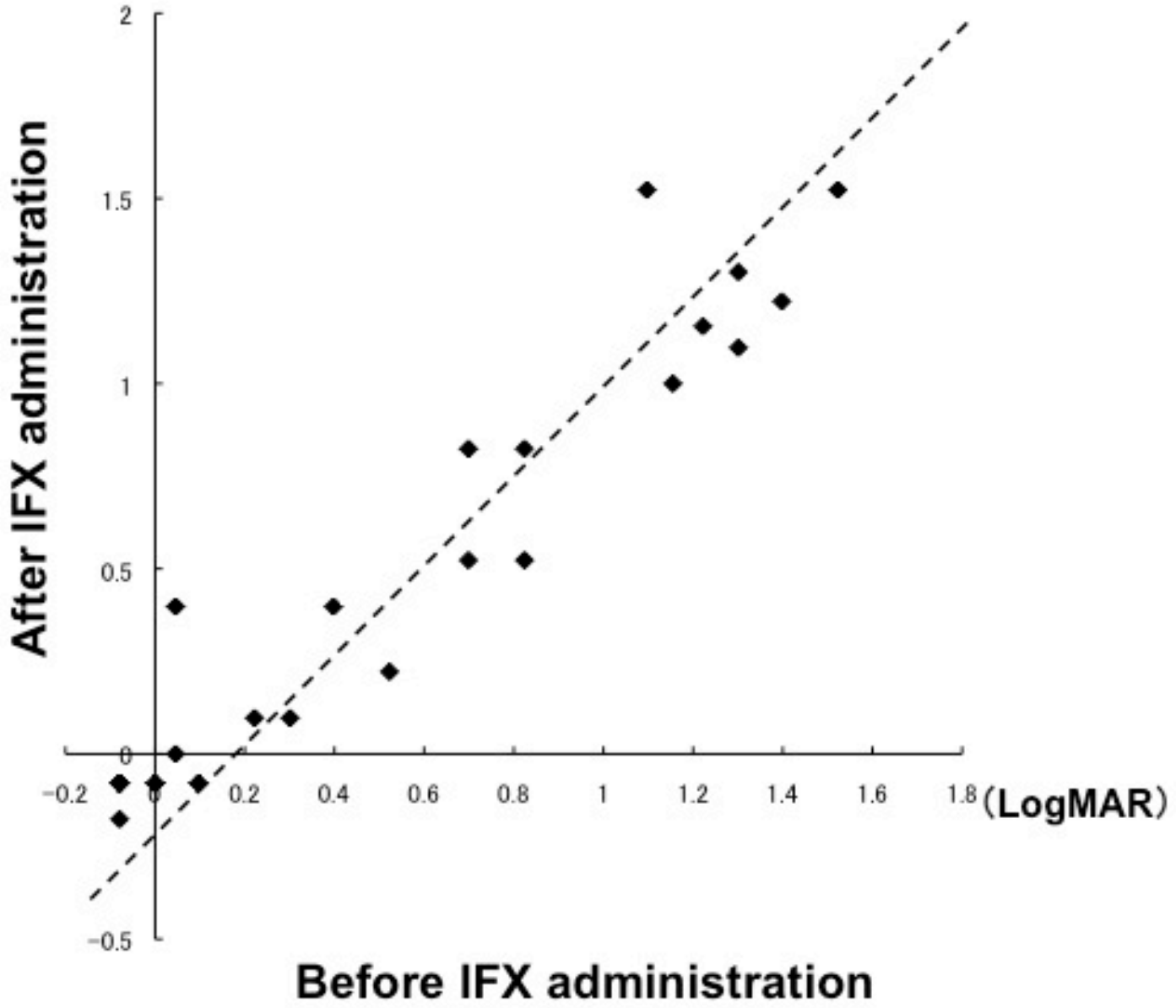
Table 1. Characteristics of Behçet's disease patients treated with IFX

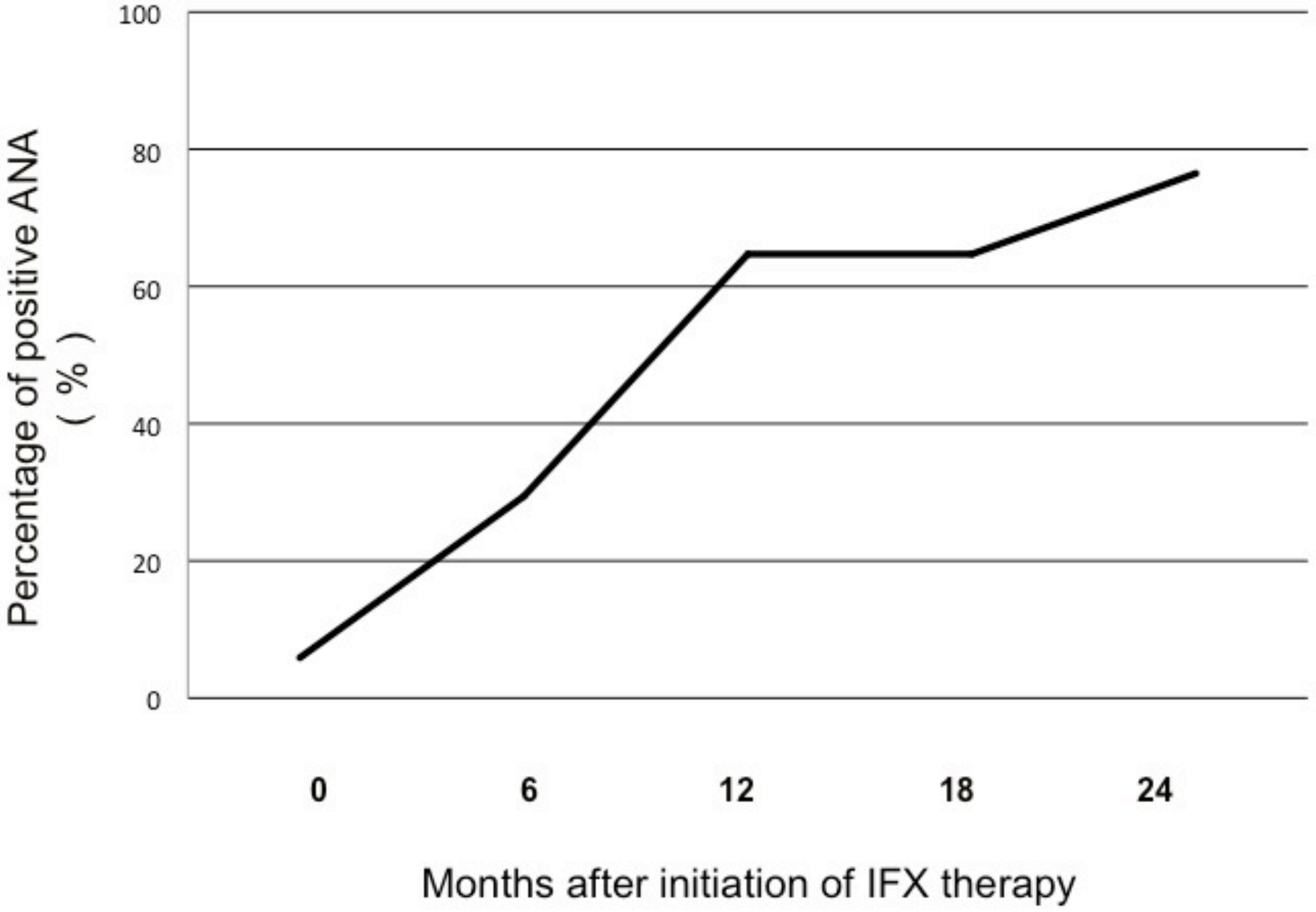
IFX – infliximab, CyA – cyclosporine A, Col – colchicine, PSL – prednisolone

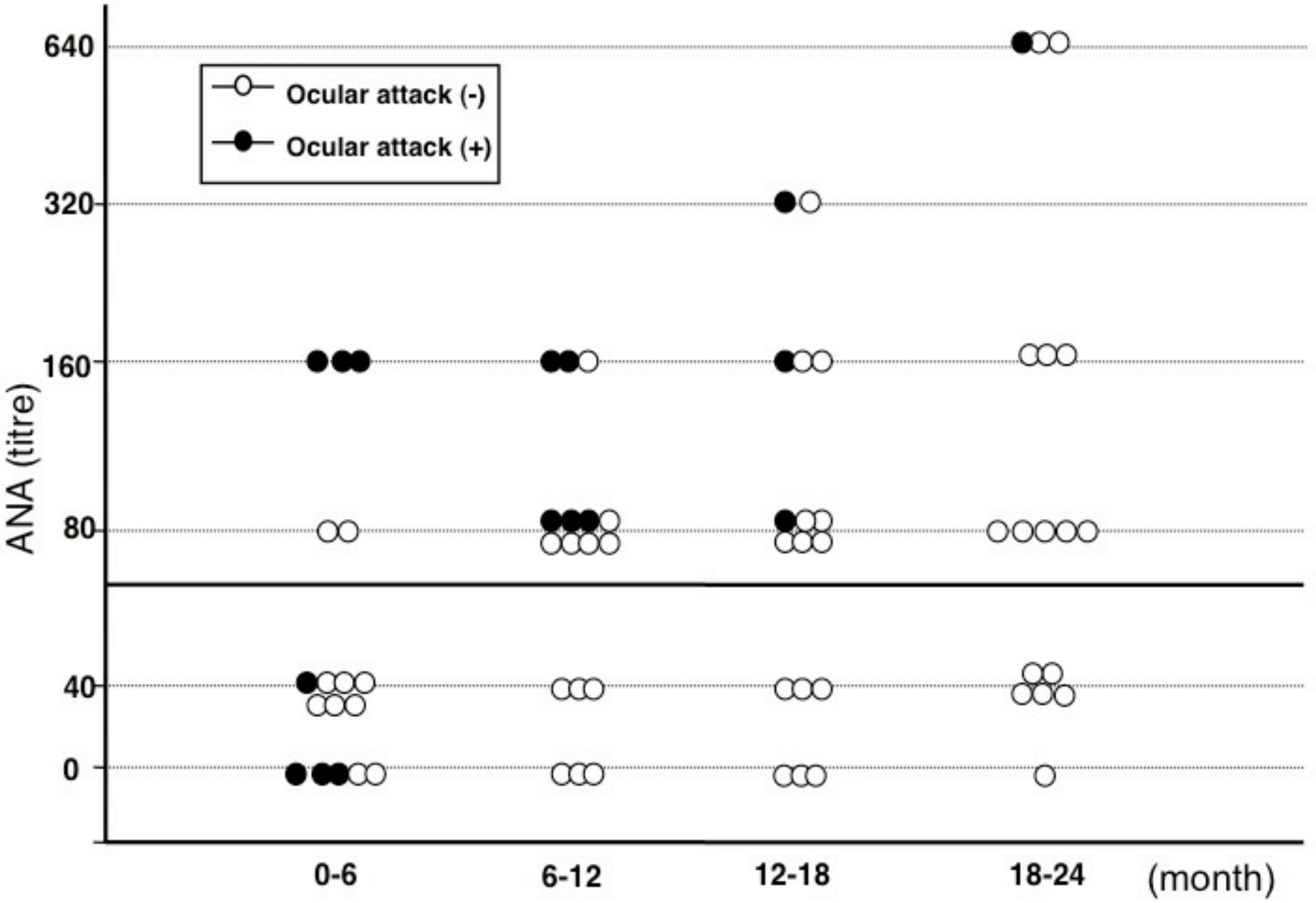
Case	Frequency of ocular attacks -6～0month	ANA (titre) 0month	Frequency of ocular attacks 0～6month	ANA (titre) 6month	Frequency of ocular attacks 6～12month	ANA (titre) 12month	Frequency of ocular attacks 12～18month	ANA (titre) 18month	Frequency of ocular attacks 18～24month	ANA (titre) 24month
1	0	0	0	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)