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【 ORIGINAL ARTICLE 】

Two-year Outcomes of Infliximab Discontinuation in Patients with Rheumatoid Arthritis: A Retrospective Analysis from a Single Center

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Abstract:

Objective To investigate the clinical outcomes of rheumatoid arthritis (RA) patients who discontinued infliximab (IFX) treatment at our hospital.

Methods Among 249 patients receiving IFX from 2007 to 2015, we retrospectively investigated the clinical courses of 18 who discontinued IFX after achieving the 28-joint disease activity score based on the erythrocyte sedimentation (DAS28-ESR) clinical remission (CR) and whose clinical courses were available continuously for 96 weeks after discontinuation.

Results At IFX introduction, the median age was 56.9 (range 36.1-72.4) years, and the disease duration was 5.2 (0.4-25.6) years. The median duration of maintaining either CR or a low disease activity (LDA) with IFX was 37.2 (4.0-91.4) months, and the total duration of IFX therapy was 45.8 (17.1-96.9) months. After discontinuation, 8 patients (44.4%) maintained CR/LDA for 96 weeks (no-flare group), and 10 (55.6%) experienced flares (DAS28-ESR≥3.2) within 96 weeks (flare group). In the no-flare group, six patients receiving intensified conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy to prevent flare ups simultaneously either with or immediately after discontinuing IFX. In the flare group, four patients received intensified csDMARD therapy. Six patients restarted biological DMARDs (bDMARDs), and all achieved CR again. Ultimately, 12 patients (66.7%) maintained a Bio-free disease control for 96 weeks. A comparison of the clinical backgrounds between the flare and no-flare groups showed no marked difference in their disease duration, IFX dosage, duration of maintaining CR with IFX, or concomitant csDMARDs use.

Conclusion Irrespective of the RA disease duration, more than half of all patients maintained a Bio-free condition for 96 weeks. Continuing LDA with IFX for a sufficiently long period of time before discontinuation and preventive intensification of csDMARD therapy may help maintain a Bio-free condition.

Key words: rheumatoid arthritis, infliximab, conventional synthetic disease-modifying antirheumatic drugs, biologics free condition, golimumab

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Introduction

Infliximab (IFX) is a chimeric human anti-tumor necrosis factor (TNF)-α monoclonal antibody which is used in biological disease-modifying antirheumatic drugs (bDMARDs) for rheumatoid arthritis (RA). Multiple TNF inhibitors are available, and the efficacy of IFX has been well demonstrated (1). On achieving clinical remission (CR), the possibility of discontinuing IFX and maintaining CR or a low disease activity (LDA)-in other words, a Bio-free condition-has been reported (2, 3). However, the actual situation con-

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cerning the achieving of a Bio-free condition in daily clinical practice has not yet been well documented.

We herein report our experience concerning patients' achieving a Bio-free condition.

Materials and Methods

Patients and methods

IFX was used in 249 RA patients (53 males and 196 females) between January 2007 and October 2015.

Among these patients, we retrospectively analyzed the clinical courses of 18 (2 males and 16 females) who discontinued IFX after achieving CR and whose clinical courses were available continuously for 96 weeks after IFX discontinuation.

All 18 patients started IFX therapy because of insufficient disease control despite receiving the maximum tolerable dose of MTX monotherapy or MTX concomitant therapy with multiple conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or prednisolone. IFX was the first bDMARD for all 18 patients. It was administered at 3 mg/kg at 0, 2 and 6 weeks and then every 8 weeks subsequently. Since the dose escalation and shortening of IFX therapy (intensification of IFX therapy) was approved in 2009, the dosage in the case of IFX intensification is described in terms of mg/kg/8 weeks (e.g., 6 mg/kg/4 weeks=12 mg/kg/8 weeks). The IFX dosage, concomitant treatment with methotrexate (MTX), csDMARDs and steroids were adjusted according to the standard medical practice for controlling disease activity at the discretion of the attending physicians.

Data on the patient characteristics, including the age, disease duration of RA, disease activity, IFX treatment duration and changes in disease activity and treatment, were collected retrospectively from the clinical records. The disease activity was assessed using the 28-joint disease activity score based on the erythrocyte sedimentation rate (DAS28-ESR) (4), and disease flare was defined as deterioration from CR/LDA (DAS28-ESR≤3.2) to moderate disease activity (3.2<DAS28-ESR≤5.1) or high disease activity (5.2<DAS28-ESR).

Written consent was not obtained, but the publication of the results was approved by the relevant ethics committees.

Decision to discontinue IFX

The decision to discontinue IFX was made by consultation and agreement between the patients and physicians. No precise criteria were established, but when patients maintained CR for more than two years, we proposed the discontinuation of IFX. If patients wished to discontinue treatment before two years' remission due to financial reasons, then we discontinued the therapy.

Statistical analyses

Variables between groups were compared by the Mann-Whitney U-test. Differences in the frequencies between groups were compared by Fisher's exact test. Continuous variables were evaluated by Wilcoxon's signed rank test. Probability values (p values) <0.05 (two-sided) were used to indicate statistical significance. All data were expressed as the median and range (minimal value - maximal value). All calculations were performed using the SPSS software program for Windows, ver. 22 (IBM, Illinois, USA).

Results

Patients' characteristics at the introduction and discontinuation of IFX

At the time of the introduction of IFX, the median age of the patients was 56.9 (36.1-72.4) years old, and the disease duration of RA was 5.2 (0.4-25.6) years. Nine patients were Steinblocker's stage III or IV (5), and the median DAS28-ESR was 5.06 (2.4-6.89), as shown in Table 1.

The dosage of IFX was intensified in 14 patients (77.8%) due to an insufficient effect before discontinuation. The median maximal dose was 6.0 (3.0-12.0) mg/kg/8 weeks.

All 18 patients achieved CR during IFX therapy, and 17 showed CR/LDA when IFX was discontinued except for 1 on MDA who strongly desired to discontinue IFX. The median total duration of IFX therapy was 45.8 (17.1-96.9) months. The rate of PSL users at IFX discontinuation significantly decreased compared to that at IFX introduction of IFX (p=0.029), and the median dose significantly decreased from 5.0 (2.0-10.0) mg/day at IFX introduction to 2.5 (1.0-5.0) mg/day at IFX discontinuation (p=0.025). The dose of MTX did not change significantly. The number of patients receiving concomitant csDMARDs other than MTX increased from 10 at the introduction of IFX (using 1 agent: 8 patients; using 2 agents: 2 patients) to 12 at the discontinuation of IFX (using 1 agent: 7 patients; using 2 agents: 4 patients; using 3 agents: 1 patient), but no significant difference was observed. At the discontinuation of IFX, the following csDMARDs were being used: tacrolimus (TAC) in five patients, bucillamine (BUC) in three patients, salazosulfapyridine (SASP) in three patients and mizoribine (MZR) in five patients. Among the 14 cases of IFX intensification, 13 discontinued IFX at the maximal dose.

Rate of maintaining CR/LDA for 96 weeks after IFX discontinuation

The rate transition of patients who maintained CR or LDA without flare is shown in Figure. Eight patients (44.4%) maintained CR/LDA for 96 weeks without flare (no-flare group); 6 were in CR, and 2 had an LDA at week 96. The other 10 patients experienced flares within 96 weeks (flare group). The median time to flare from IFX discontinuation was 5.5 (2.0-21.0) months.

Changes in the treatment in the no-flare group

Changes in the treatment from IFX introduction to 96 weeks after IFX discontinuation in the no-flare group are

Table 1. Patients' Characteristics at the Induction and Discontinuation of IFX.

	At the introduction of IFX (n=18)	At the discontinuation of IFX (n=18)	p value
Age (years)	56.9 (36.1-72.4)	61.8 (39.0-75.9)	<0.01
Female, n (%)	16 (88.9)	16 (88.9)	1.0
Disease duration (years)	5.2 (0.4-25.6)	8.4 (2.4-28.7)	<0.01
RF-positive, n (%)	14 (77.8)	7 (38.9)	0.041*
RF (IU/mL)	26.5 (5.0-704.0)	12.5 (5.0-81.0)	<0.01
ACPA-positive, n (%)	14 (77.8)	-	
Steinblocker's stage I/II/III/IV (% of III+IV)	0/9/4/5 (50.0)	0/9/4/5 (50.0)	1.0
Tender joint count (0-28)	4 (0-28)	0 (0-10)	<0.01
Swollen joint count (0-28)	7 (0-28)	0 (0-1)	<0.01
ESR (mm/h)	40.0 (2.0-91.0)	7.5 (4.0-23.0)	<0.01
CRP (mg/dL)	2.75 (0.1-9.0)	0.1 (0.0-0.3)	<0.01
DAS28-ESR	5.06 (2.40-6.89)	1.69 (1.25-3.75)	<0.01
MTX dose (mg/week)	8.0 (4-12)	8.0 (4.0-12.0)	0.898
PSL use, n (%)	13 (72.2)	8 (44.4)	0.029*
PSL dose of users (mg/day)	5.0 (2.0-10.0)	2.5 (1.0-5.0)	0.025*
csDMARD use (except for MTX), n (%)	10 (55.6)	12 (66.7)	0.563
Number of csDMARDs except for MTX 0/1/2/3 (% of more than 2 agents)	8/8/2/0 (11.1)	6/7/4/1 (27.8)	0.402
Two or more csDMARD use (other than MTX), n (%)	2 (11.1)	5 (27.8)	0.490
IFX treatment			
Maximal IFX dosage (mg/kg/8 weeks)		6.0 (3.0-10.0)	
Total duration of IFX therapy (months)		45.8 (17.1-96.9)	

Results are shown as the median (range: minimum-maximum).

*p≤0.05 in the Mann-Whitney U test or Fisher's exact test.

ACPA: anti-citrullinated protein antibodies, csDMARDs: conventional synthetic disease-modifying antirheumatic drugs, CR/LDA: clinical remission or low disease activity, CRP: C-reactive protein, DAS: disease activity score, ESR: erythrocyte sedimentation rate, IFX: infliximab, MTX: methotorexate, PSL: prednisolone, RF: rheumatoid factor

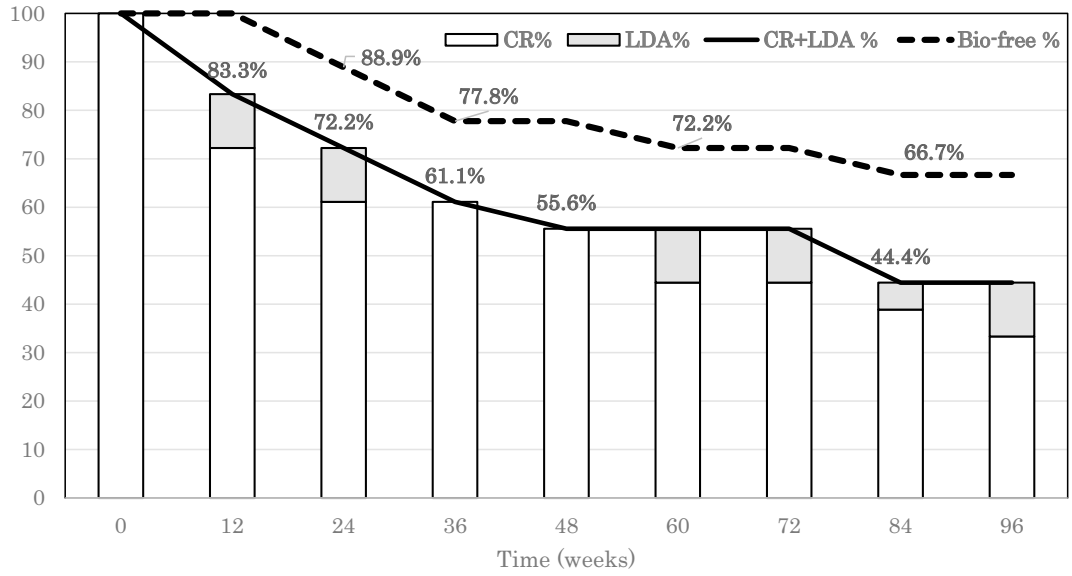

Figure. Proportion changes in a sustained Bio-free condition and CR/LDA without flare after IFX discontinuation. The white and black bar graphs show the proportion of patients who maintained clinical remission (CR) and a low disease activity (LDA), respectively. The solid line indicates the change in the proportion of total patients maintaining CR and LDA. The broken line indicates the change in the proportion of patients maintaining a Bio-free condition. The horizonal axis indicates the time from the discontinuation of IFX. IFX: infliximab

Table 2. Changes in the Treatment in the No-flare Group.

Case	At the introduction of IFX			At the discontinuation of IFX			Total duration of IFX therapy (months)	Preventive csDMARDs intensification	At week 96		
	MTX	PSL	csDMARDs	MTX	PSL	csDMARDs			MTX	PSL	csDMARDs
1	8.0	10.0	SASP, MZR	10.0	5.0	SASP	96.9	Addition (TAC, MZR)	10.0	5.0	SASP, TAC, MZR
2	8.0	5.0	-	6.0	0.0	-	69.9	Addition (SASP)	0.0 (liver dysfunction)	0.0	SASP
3	8.0	4.0	SASP	4.0	1.0	-	44.8	Addition (BUC)	4.0	1.0	BUC
4	8.0	0.0	-	6.0	0.0	T	68.5	-	0.0 (lymphadenopathy)	0.0	TAC
5	12.0	2.0	MZR	10.0	2.0	MZR, TAC, BUC	38.0	-	10.0	2.0	BUC, TAC, MZR
6	8.0	7.0	TAC	8.0	0.0	-	41.2	MTX 8→10, Addition (MZR)	10.0	0.0	MZR
7	8.0	8.0	BUC	12.0	4.0	SASP	59.3	MTX 12→16, Addition (MZR)	16.0	4.0	SASP, MZR
8	8.0	0.0	-	6.0	0.0	BUC	42.3	MTX 6→8	8.0	0.0	BUC

BUC: bucillamine, csDMARDs: conventional synthetic disease modified anti-rheumatic-drugs, MTX: methotrexate (mg/week), MZR: mizoribine, PSL: prednisolone (mg/day), SASP: salazosulfapyridine, TAC: tacrolimus

shown in Table 2. CsDMARD therapy was intensified in six patients in the no-flare group, except for only two patients (cases 4 and 5), to prevent flare simultaneously either with or immediately after IFX discontinuation as follows: MTX dose intensification in one patient, addition of the csDMARDs in three patients and both of them in two patients. Case 4 had to stop MTX due to suspicion of MTX-associated lymphoproliferative disease, and Case 5 had received three csDMARDs other than MTX already before IFX discontinuation, so the therapy was not preventively intensified.

Changes in the treatment in the flare group and the rate of maintaining a Bio-free condition for 96 weeks after IFX discontinuation

Changes in the treatment in the flare group are shown in Table 3. The median DAS28-ESR at flare was 3.9 (3.3-5.6), and the median duration from IFX discontinuation to flare was 5.5 (2.0-21.0) months. After flare up, csDMARD therapy was intensified in seven patients, while the other three required the re-introduction of bDMARD therapy. Two patients wished to have bDMARDs re-introduced prior to csDMARD intensification.

Ultimately, 12 of the 18 total patients (66.7%) maintained a Bio-free condition for 96 weeks (Figure). The median Bio-free duration of the 6 patients who restarted bDMARDs was 6.9 (2.7-20.8) months. IFX was resumed in only 1 of these patients (4 mg/kg/4 weeks), and golimumab (GLM) was started in the other 5 patients (4 patients: 100 mg/4 weeks, 1 patient: 50 mg/4 weeks).

When IFX was discontinued, the intensification of csDMARD treatment was considered in order to prevent the reintroduction of bDMARDs mainly for patients who used only one csDMARD other than MTX or who had difficulty tolerating an increased MTX dose due to adverse events, with reference to a previous report on the efficacy of addition of csDMARDs (6). Intensification was performed in six patients within two months after IFX discontinuation while maintaining LDA at the discretion of the attending rheumatologist, as shown in Table 3. Even though preventive intensification of the therapy, three of them (cases 9, 15 and 16; Table 3) required the reintroduction of bDMARDs. Although case 9 received more than 8 mg weekly of MTX and 2 csDMARDs, flare occurred after only 6 months, and IFX was restarted after 7.4 months. In case 15, flare was ultimately observed, but a Bio-free condition was maintained for 21 months. In case 16, csDMARD intensification was insufficient due to liver dysfunction, and IFX was restarted after 6.5 months.

In contrast, another four patients also considered preventive csDMARDs intensification but did not receive it, as cases 12 and 14 had stopped BUC and SASP due to adverse events, and cases 17 and 18 were already receiving the maximum tolerable dose of MTX with two other agents. In case 18, the addition of csDMARDs had been actively attempted to decrease the PSL dose before IFX discontinuation. As a result, three of them (cases 14, 17 and 18) resumed bDMARDs. Case 18 was the only patient who discontinued IFX under unstable disease control. It took for him 61 months to achieve CR since the introduction of IFX, and IFX was discontinued after only 4 months due with his strong wishes. After IFX discontinuation, an LDA was maintained for 3 months, but he experienced flare up only 5 months later, and his DAS28-ESR worsened to 5.58.

Table 3. Changes in the Treatment in the Flare Group.

Case	At the introduction of IFX			At the discontinuation of IFX			Total duration of IFX therapy (months)	Preventive treatment intensification	Duration from Discontinuation to flare (months)	After flare			
	MTX	PSL	csDMARDs	MTX	PSL	csDMARDs				csDMARDs intensification	bDMARDs readministration	Duration of Bio-free (months)	Duration from flare to re-achieving CR (weeks)
9	8.0	0.0	TAC	8.0	0.0	TAC	85.7	MTX8→10, Addition (MZR)	6	-	GLM (100mg/4weeks)	7.4	4.0
10	4.0	5.0	-	4.0	2.0	-	17.1	Addition (MZR)	3	MTX 4→8, Addition (TAC), Increment (MZR)	-		24.0
11	8.0	2.5	BUC	7.0	0.0	BUC	47.5	Addition (MZR)	21	MTX64→7, Increment (MZR)	-		8.0
12	10.0	0.0	-	12.0	4.0	MZR	23.4	-	6	Addition (IGU)	-		25.7
13	8.0	0.0	-	8.0	0.0	-	54.6	Addition (MZR)	10	MTX84→10, Addition (PSL5)	-		4.7
14	12.0	5.0	TAC	6.0	2.5	TAC, MZR	32.0	-	2	MTX64→8, Addition (IGU)	GLM (100mg/4weeks)	2.8	4.0
15	8.0	5.0	-	8.0	4.0	-	26.4	Addition (MZR)	18	MTX84→10	GLM (50mg/4weeks)	20.8	4.0
16	8.0	5.0	SASP, TAC	6.0	0.0	-	46.8	Addition (MZR)	5	MTX64→8	IFX (4mg/kg/8weeks)	6.5	4.0
17	8.0	0.0	SASP	8.0	0.0	SASP, MZR	33.8	-	3	-	GLM (100mg/4weeks)	3.8	5.0
18	6.0	5.0	-	9.0	1.0	TAC, MZR	65.1	-	5	Increment (TAC, PSL14→3.5)	GLM (100mg/4weeks)	13	unknown

BUC: bucillamine, CR: clinical remission, csDMARDs: conventional synthetic disease modified anti-rheumatic-drugs, GLM: golimumab, IFX: infliximab, IGU: iguratimod, MTX: methotrexate (mg/week), MZR: mizoribine, PSL: prednisolone (mg/day), SASP: salazosulfapyridine, TAC: tacrolimus

We investigated the clinical course after flare up. One patient (case 18) was transferred to another hospital after GLM introduction, so the clinical course of 9 of the 10 patients in the flare group were available. After flare up, 9 patients achieved CR again. The median duration from csDMARD intensification to re-achieving CR in the 4 patients who did not restart bDMARDs (cases 10-13 in Table 3) was 4.7 (4.7-25.7) weeks. The median duration from the readministration of bDMARDs to re-achieving CR in 5 patients was 4.0 (4.0-5.0) weeks. These findings indicate that the administration of IFX or GLM for the first time led to re-achieving CR.

On further observation, two patients who resumed bDMARDs (cases 14 and 16 in Table 3) achieved a Bio-free condition again. Case 14, who restarted GLM (100 mg/4 weeks) because of an insufficient of intensification of csDMARD therapy (addition of IGU to MZR and TAC), discontinued GLM again after 12 months, and a Bio-free condition was maintained for over 1 year without re-flare with the concomitant use of MTX, MZR, TAC and IGU. Case 16 discontinued IFX again after 12 months. Although flare was observed at week 25 after the re-discontinuation of IFX, CR was achieved again due to the addition of IGU and increment of MTX (8 to 9 mg weekly), and a Bio-free condition was maintained for over 3 years. In this patient, MTX over 8 mg weekly had not yet been approved when IFX was restarted.

Comparing the parameters between the no-flare group and the flare group

We compared the background characteristics between the no-flare and flare groups, as shown in Table 4. However, no significant differences were noted in any parameters, including the disease duration of RA, time to CR achievement from the introduction of IFX, duration of maintained CR/LDA with IFX, total duration of IFX therapy, maximum IFX dosage and concomitant MTX, PSL and csDMARDs use.

Discussion

In our experience, among the 18 RA patients who discontinued IFX, 44% maintained LDA, and 67% ultimately maintained a Bio-free condition for 96 weeks.

Several studies have described the possibility of maintaining a Bio-free condition after achieving remission with IFX. The BeST study, which focused on patients with early RA, reported that 5 years after the discontinuation of IFX, 19% maintained a Bio-free condition (2). Nawata reported 9

Table 4. A Comparison of the Clinical Background Characteristics and the Laboratory Parameters between the No-flare Group and Flare Group.

	No-flare group (n=8)	Flare group (n=10)	p value
Female, n (%)	6 (75.0)	10 (100)	0.183
Steinblocker's stage III/IV, n (%)	3 (37.5)	6 (60.0)	0.319
At the introduction of IFX			
Age (years)	55.6 (36.0-72.4)	58.9 (36.1-72.1)	0.696
Disease duration (years)	2.5 (0.4-25.6)	5.6 (1.1-7.7)	0.055
RF-positive, n (%)	6 (75.0)	8 (80.0)	0.197
RF (IU/mL)	26.0 (5.0-309)	36.0 (12-704)	0.79
ACPA-positive, n (%)	7 (87.5)	7 (70.0)	0.558
ESR (mm/h)	42.0 (11.0-81.0)	38.0 (2.0-91.0)	0.360
CRP (mg/dL)	2.35 (0.1-5.6)	3.35 (0.1-9.0)	0.965
DAS28-ESR	4.68 (2.40-6.82)	5.71 (2.47-6.89)	0.515
MTX dose (mg/week)	8.0 (8.0-12.0)	8.0 (4.0-12.0)	0.696
PSL use, n (%)	6 (75.0)	7 (70.0)	0.618
PSL dose of users (mg/day)	6.0 (2.0-10.0)	5.0 (2.0-5.0)	0.366
csDMARD use (other than MTX), n (%)	5 (62.5)	5 (50.0)	
Two or more csDMARD use (other than MTX), n (%)	1 (12.5)	1 (10.0)	0.706
Time to CR achievement from IFX introduction (months)	3.8 (1.6-30.2)	8.0 (2.4-61.1)	0.203
Duration maintained CR/LDA with IFX (months)	41.5 (29.1-91.4)	24.1 (4.0-74.2)	0.055
Total duration of IFX administration (months)	52.0 (38.0-96.9)	40.3 (17.1-85.7)	0.173
Dose intensification of IFX, n (%)	5 (62.5)	9 (90.0)	0.412
Maximum IFX dosage (mg/kg/8weeks)	5.5 (3.0-10.0)	6.0 (4.0-10.0)	0.696
At the discontinuation of IFX			
Age (years)	59.8 (39.0-75.9)	63.3 (39.7-73.4)	0.573
Disease duration (years)	6.9 (3.9-28.7)	8.8 (2.4-14.3)	0.505
ESR (mm/h)	7.0 (5.0-23.0)	9.0 (4.0-23.0)	0.829
CRP (mg/dL)	0.1 (0.0-0.1)	0.1 (0.1-0.3)	0.173
DAS28-ESR	1.56 (1.25-2.23)	1.88 (1.25-3.75)	0.315
MTX dose (mg/week)	8.0 (4.0-12.0)	8.0 (4.0-12.0)	0.965
PSL use, n (%)	3 (37.5)	5 (50.0)	0.681
PSL dose of users (mg/day)	3.0 (1.0-5.0)	2.5 (1.0-4.0)	0.905
CsDMARD use (other than MTX), n (%)	4 (50.0)	7 (70.0)	
Two or more csDMARD use (other than MTX), n (%)	1 (12.5)	3 (30.0)	0.618

Results are shown as the median (range: minimum-maximum).

*p≤0.05 in Mann-Whitney U test or Fisher's exact test.

RF: rheumatoid factor, csDMARDs: conventional synthetic disease modified anti-rheumatic-drugs, CR/LDA: clinical remission or low disease activity, CRP: C-reactive protein, DAS: disease activity score, ESR: erythrocyte sedimentation rate, IFX: infliximab, MTX: methotorexate, PSL: prednisolone

cases who successfully discontinued IFX and maintained remission for 6-29 months (7). In the IDEA study, of the 14 patients who stopped IFX therapy after achieving sustained remission (>6 months), 11 (78.6%) maintained remission for a further 6 months (8). These studies especially focused on patients with early RA and indicated that a short disease duration and sustained LDA are important factors for maintaining Bio-free disease control. However, in contrast to these previous studies, the median disease duration in our subjects exceeded eight years when IFX was discontinued. Tanaka et al. reported the outcomes among established RA patients in the RRR (remission induction by Remicade in RA) study (3). In their study, the mean patient age was 51.4 years, and the mean disease duration was 5.9 years. At 1 year after IFX discontinuation, 55% of the patients had maintained CR/LDA, and 68.6% had maintained a Bio-free condition. Those patients' background characteristics and the results of maintaining a Bio-free condition were equivalent to our own. The results of the RRR study may therefore have been reproduced in the real world according to our retrospective study. In terms of the factors related to achieving RRR, they concluded that a younger age and shorter disease duration were important. However, our data did not show any significant differences between the flare and no-flare groups, possibly because the samples were limited and the age and disease duration had a wide range. The RRR study also concluded that deep remission (DAS28 ≤2.22) made it possible to maintain an LDA for 1 year in 71.4% of the patients. In our study, the DAS28-ESR of 16 patients (88.9%) was <2.2 at the discontinuation of IFX. One patient who stopped IFX despite a moderate disease response experienced flare after only five months. It was speculated that

flare had accelerated not only because of the poor disease activity but also because of the short CR maintenance period. Deep remission and a sufficient CR maintenance period with IFX prior to IFX discontinuation may also be factors for successful Bio-free control. Recently, the multibiomarker disease activity (MBDA) has received attention as reflecting the current disease activity along with changes and the treatment response (9). Futhermore, the MBDA was also reported to be a potential predictor of flare after the discontinuation of TNF inhibitors (10). While the measurement of biomarkers included in the MBDA remains relatively uncommon and data are lacking at present, such objective predictors are expected to be established in the future.

One point that differed between the RRR study and our own was that IFX was discontinued after only 24 weeks of maintaining LDA in the RRR study. We did not follow any particular protocol regarding the discontinuation of IFX, so the median duration of maintained LDA was 41.5 months in the no-flare group and 24.1 months in the flare group. It may be reasonable to suggest that patients stop IFX earlier, as in the RRR study.

One point of note in the present study is that some patients received intensified csDMARD therapy to prevent flare. Six of the eight patients without flare received intensified csDMARD therapy. The usefulness of triple-combination therapy for inducing remission has been previously reported (11, 12). Kurasawa et al. reported the efficacy of adding another csDMARD to reduce the flare rate after the discontinuation of IFX (6). We also previously reported the importance of the additional administration of csDMARDs to obtain a good outcome after the discontinuation of adalimumab (13). In our study, four patients who experienced flare achieved remission again and maintained a Bio-free condition with the addition of csDMARDs. Naniwa et al. reported the efficacy of adding TAC to maintain remission after the discontinuation of TNF inhibitor therapy (14). Though our limited data are not sufficient to discuss the efficacy of preventive csDMARD intensification, the concomitant use of sufficient csDMARDs may be a useful strategy at the discontinuation of IFX.

In terms of the IFX dose, no significant difference was shown between the flare and no-flare groups. Hidaka et al. (15) and Kobayashi et al. (16) reported that IFX dose escalation was effective in cases of discontinuation of IFX. In contrast, Tanaka et al. reported that raising-dose of IFX strategy based on the baseline levels of serum TNF-α did not increase the sustained remission rate after IFX discontinuation in the RRRR study (17). The most effective way of increasing the IFX dose with the goal of achieving a Bio-free status in the future is unclear; however, ensuring that the dose is sufficient to achieve deep remission may be ideal.

When we focused on the flare cases in our study, it turned out that GLM was effective for immediately achieving CR again. Usually, it takes time to achieve CR with GLM (18), but in our cases, GLM induced CR with the first injection. We often suggest the discontinuation of IFX when a patient is maintaining CR. However, some patients are reluctant to discontinue IFX due to fears of relapse. In addition, the re-injection of IFX carries a risk of a severe infusion reaction (19). However, if we adequately explain these findings to patients, we may be able to encourage them to discontinue IFX without anxiety. In addition, GLM may be an acceptable choice due to the fact that patients will not have to inject it by themselves.

Several limitations associated with the present study warrant mention. First, this study was not a prospective one but a report of an experience at a single center. We did not have a fixed protocol for discontinuing IFX, so we cannot accurately discuss the factors associated with a Bio-free condition. Second, most of the patients (n=16) had IFX introduced before permission to use more than 8 mg of MTX weekly had been approved in Japan. They may therefore have not needed bDMARDs if they had received enough MTX. However, we often experience intolerance to high-dose MTX, so our results may be useful in a real-world setting.

Conclusion

In our experience, when patients discontinue IFX after a long maintenance of CR/LDA, more than half maintained a Bio-free condition for 96 weeks. Furthermore, adding csDMARDs was effective for maintaining Bio-free control or re-achieving CR after flare.

The authors state that they have no Conflict of Interest (COI).

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