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ORIGINAL ARTICLE

Discontinuation of infliximab in rheumatoid arthritis patients in clinical remission

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Abstract Biologic drugs are effective but are also expensive, and it is difficult to evaluate the duration of treatment. Infliximab, an anti-TNFα antibody, suppresses arthritic activity and inhibits bone destruction in patients with rheumatoid arthritis (RA). Here, we document that infliximab could be discontinued after clinical remission in RA patients. Among 172 patients with RA who reached clinical remission following infliximab (3 mg/kg) and methotrexate (MTX, >6 mg/w), nine patients with sustained remission discontinued it. Clinical assessment was based on a disease activity score (DAS) that included a 28-joint count/erythrocyte sedimentation rate (DAS28-ESR). The disease was assessed before and after the start of infliximab treatment, and concomitant drug treatment—in the order of corticosteroid, nonsteroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs) other than MTX—was gradually discontinued. We considered patients for discontinuation of infliximab treatment after remission (DAS28-ESR < 2.6) had been sustained for more than 24 weeks. The nine patients able to discontinue treatment were all females, with a mean age of 53.8 years; eight patients were at stage I or II. The mean duration of disease was 28.7 months, and these patients were on corticosteroid treatment equivalent to a mean of 2.28 mg prednisolone (PSL). These nine patients all met the remission standard—that DAS28-ESR < 2.6 for $\geq$24 weeks) —and so their treatment with concomitant drugs was discontinued. After the discontinuation of infliximab, the mean period of sustained remission was 14.2 months and the longest period was 29 months. The duration of disease was significantly shorter and the points from Steinbrocker's stage-classification were significantly lower in the infliximab-discontinued group than in the infliximab-continued group. Strategic reductions and/or discontinuations of concomitant treatment were performed in RA patients who attained clinical remission (DAS28 < 2.6) through treatment with infliximab and MTX. Nine patients successfully discontinued infliximab after maintaining clinical remission for more than 24 weeks. After infliximab was discontinued, clinical remission and suppression of joint destruction were maintained with MTX alone, especially in early RA patients.

Keywords Rheumatoid arthritis · Infliximab · Remission · Discontinuation

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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disorder of unknown etiology. Its major distinctive feature is chronic, symmetric and erosive synovitis, and the severity of the joint disease may fluctuate over time, but the most common outcome of the established disease is the progressive development of various degrees of joint destruction, deformity, and disability. Tumor necrosis factor (TNF)-α produced in RA synovial tissue contributes to the synovitis and bone destruction [1–4]. Clinical trials of RA have demonstrated that TNF blockade with agents such as infliximab, an anti-TNF-α chimeric antibody, and etanercept, a soluble TNF receptorimmunoglobulin (Ig) fusion protein were efficacious in the treatment of RA. These molecules not only markedly improve clinical signs

and symptoms but they also inhibit joint destruction, as reported in the Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) study [5–7], the Active Controlled Study of Patients Receiving Infliximab for Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) [8], and for etanercept in the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) study [9–11]. Furthermore, in the BeSt (Dutch acronym for Behandel–Strategieen, "treatment strategies") study conducted in Europe, infliximab was combined with MTX for 120 RA patients with high disease activity within two years of onset. Within two years of treatment, 77 patients discontinued infliximab after maintaining clinical remission, as estimated by disease activity score (DAS) 28-ESR < 2.6, for more than 24 weeks. Of these patients, 66 had sustained remission for at least one more year of discontinuation, demonstrating that infliximab may induce remission, even in highly active diseases [12].

Once we have obtained clinical remission in patients treated with infliximab, the subsequent aim is the successful and safe discontinuation of infliximab, because of issues associated with cost and very long-term safety in relation to infection and malignancy. However, no guidelines have been proposed for the discontinuation of infliximab in RA patients exhibiting maintained clinical remission. In this study, we document the strategic reduction and/or discontinuation of concomitant treatment in nine RA patients who attained clinical remission via infliximab and MTX treatment.

Materials and methods

Patients

Infliximab was administered to patients that met the 1987 American College of Rheumatology (ACR) diagnostic criteria for RA. We registered 172 active RA patients who met the criteria of $\geq$6 tender joints, $\geq$6 swollen joints, C-reactive protein (CRP) of $\geq$2.0 mg/dl or erythrocyte sedimentation rate (ESR) of $\geq$28 mm/h, despite receiving MTX for at least four weeks prior to the introduction of infliximab. MTX treatment was maintained at the same dose for at least four weeks before the initiation of infliximab. Corticosteroid and nonsteroidal anti-inflammatory drugs (NSAIDs) were started or remained unchanged within at least four weeks before infliximab induction. Infliximab was infused to patients at 0, 2 and 6 weeks, followed by every eight weeks, at 3 mg/kg. The 172 patients were: 20 males and 152 females; aged 19–80 years (mean age of 54.1 years); Steinbrocker's classification stage I: 7.6%, stage II: 41.3%, stage III: 22.7%, and stage IV: 28.4% of the patients; the mean duration of illness was 115.5 months. The mean corticosteroid dose was equivalent to 2.83 mg of prednisolone (PSL).

Discontinuation strategy

MTX or other concomitant disease-modifying antirheumatic drugs (DMARDs) and NSAIDs used at the start of infliximab treatment were kept unchanged until the fourth infusion (at 14 weeks). After the induction and maintenance of clinical remission (DAS28 < 2.6), we tried to discontinue infliximab by performing the following strategic and sequential steps. Depending on the level of disease activity, corticosteroid and/or NSAIDs were initially reduced and discontinued, DMARDs other than MTX were stopped, and then, after clinical remission (DAS28-ESR < 2.6) had been maintained for more than 24 weeks, the discontinuation of infliximab was considered. Consequently, nine patients discontinued infliximab after we obtained informed consent from each patient. All nine patients had sustained remission for at least 24 weeks of discontinuation.

Clinical and laboratory assessments

Clinical signs used as assessment items were morning stiffness, number of tender joints (maximum 68), and number of swollen joints (maximum 66); as well as blood levels of CRP, ESR, rheumatoid factor (RF), and matrix metalloproteinase-3 (MMP-3). In addition, the patient's global assessment of disease activity (0–100 mm) was measured. Disease activity was assessed by DAS28-ESR.

Radiographic evaluation

The assessment of joint destruction was performed using Steinbrocker's classification and the van der Heijde modification of the Sharp scoring system. Effects of treatment on articular damage were assessed by evaluating radiographs of the hands and the feet for both erosions and joint-space narrowing, according to the van der Heijde modification of the Sharp scoring system [13–15]. Scores on this scale can range from 0 to 440. The reliability of this method has been documented previously [14]. Anteroposterior radiographs of the hands and feet were obtained at the discontinuation of infliximab and one year after the discontinuation of infliximab. Four readers scored the films independently.

Statistical analysis

The values are expressed as means $\pm$ SD of the number of indicated patients. Differences between two groups were examined for statistical significance by an unpaired Student

t-test. A *P* value of less than 0.05 denoted the presence of a statistically significant difference.

Results

Characteristics of RA patients that could discontinue infliximab treatment after remission

In the combination therapy of infliximab with MTX, 52 RA patients out of the 172 (30.2%) enrolled met the remission criteria of DAS28-ESR < 2.6 after 24 weeks (or approximately six months), and 34.9% (60 out of 172) did so after 12 months of the treatment. After the remission, infliximab was successfully discontinued for more than 24 weeks in nine of these RA patients, as shown in the changes in DAS28-ESR score in Fig. 1. These nine patients maintained remission with MTX 8 mg/w monotherapy for 6–29 months (mean of 14.2 months) without recurrence.

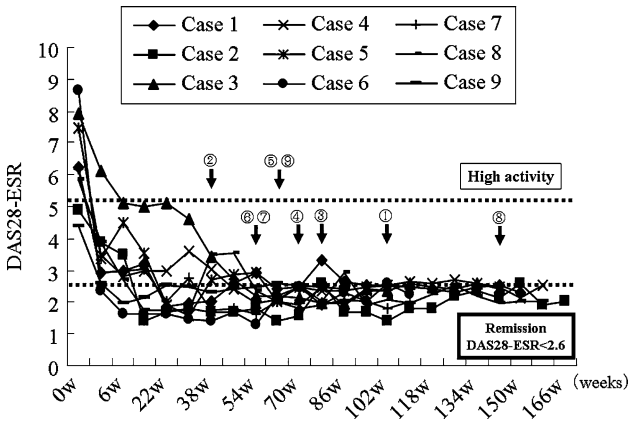

Fig. 1 Changes in the DAS28-ESR scores of nine RA patients who discontinued infliximab after the induction/maintenance of clinical remission. Each *downward arrow* shows that infusion of infliximab was discontinued. *DAS28-ESR*, disease activity score including a 28-joint count/erythrocyte sedimentation rate. The *horizontal broken lines* indicate DAS28 scores (*upper line*: 5.1 and *lower line*: 2.6)

The background characteristics of the nine patients were able to discontinue infliximab are shown in Tables 1, 2 and 3. All of the patients were female; aged 43–67 years (mean of 53.8 years); Steinbrocker's classification-stage I: 1 patient, stage II: 7 patients, and stage III: 1 patient. The duration of illness was 13–55 months (mean of 28.7 months) and most (8 of 9) of the patients had durations of less than three years. Concomitant drugs included low-dose corticosteroids (maximum of 5 mg/day and mean of 2.28 mg/day in six patients) and a DMARD (sulfasalazine (SSZ) in two patients). Depending on the level of disease activity, concomitant PSL and/or NSAIDs were initially reduced and discontinued, and subsequently DMARDs other than MTX were stopped. Infliximab treatment was given 6–20 times (mean of 11.8 times) prior to remission, with differences observed depending on the concomitant drug used.

Comparison of the backgrounds of patients who discontinued infliximab with the backgrounds of those who did not

Next, the background characteristics of nine patients who successfully discontinued infliximab after the induction and maintenance of remission were statistically compared with those of the 163 patients who could not (Table 3). There was no significant difference between these groups in terms of age, tender and swollen joint counts, CRP, ESR, RF, MMP-3, DAS28-ESR, or doses of PSL or MTX. However, the duration of disease was significantly shorter in the infliximab-discontinued group (28.7 ± 12.5 months) than in the infliximab-continued group (120.0 ± 113.1 months, $P = 0.017$). Also, the average points from Steinbrocker's stage-classification were lower in the infliximab-discontinued group (2.0 ± 0.5) than in the infliximab-continued group (2.8 ± 1.0, $P = 0.021$).

We also observed that the progression of joint destruction, as measured by the modified Sharp score, was

Table 1 The backgrounds of the nine patients that discontinued infliximab treatment (part I)

	Age (years)	Sex	Stage	Class	Disease duration (months)	DAS 28-ESR	No. of infusion	Duration of remission after stopping infliximab (months)
Case 1	45	F	II	2	30	6.24	15	11
Case 2	43	F	II	2	27	4.86	6	29
Case 3	55	F	II	2	17	7.90	13	16
Case 4	56	F	II	2	22	7.48	12	16
Case 5	63	F	III	2	35	7.50	11	20
Case 6	63	F	I	2	23	8.63	9	12
Case 7	44	F	II	2	13	6.20	9	12
Case 8	67	F	II	2	55	5.87	20	6
Case 9	48	F	II	2	36	4.40	11	6

Table 2 The backgrounds of the nine patients that discontinued infliximab treatment (part II)

	Concomitant drugs with infliximab			
	Before infliximab			After discontinuation of infliximab
Case 1	MTX 8 mg/W	SASP 1,000 mg	PSL 5 mg	MTX 8 mg/W
Case 2	MTX 8 mg/W	PSL 1 mg		MTX 8 mg/W
Case 3	MTX 8 mg/W	PSL 4 mg		MTX 8 mg/W
Case 4	MTX 8 mg/W			MTX 8 mg/W
Case 5	MTX 8 mg/W	PSL 3 mg		MTX 8 mg/W
Case 6	MTX 8 mg/W	SASP 1,000 mg	PSL 5 mg	MTX 8 mg/W
Case 7	MTX 8 mg/W			MTX 8 mg/W
Case 8	MTX 8 mg/W	PSL 2.5 mg		MTX 8 mg/W
Case 9	MTX 8 mg/W			MTX 8 mg/W

Table 3 Comparison study of the backgrounds of patients who discontinued infliximab versus those who did not

	Infliximab-discontinued group $N = 9$	Infliximab-continued group $N = 163$	P value
Age (years)	53.8 ± 9.2	54.2 ± 12.8	0.930
Duration of disease (months)	28.7 ± 12.5	120.0 ± 113.1	0.017
Steinbrocker stage classification	2.0 ± 0.5	2.8 ± 1.0	0.021
No. of tender joints (range 0–68 joints)	22.0 ± 11.8	15.9 ± 9.0	0.053
No. of swollen joints (range 0–66 joints)	16.2 ± 10.4	13.7 ± 7.6	0.336
Serum C-reactive protein (mg/dl)	3.3 ± 3.8	3.0 ± 3.0	0.729
Erythrocyte sedimentation rate (mm/h)	52.7 ± 32.3	52.9 ± 28.9	0.978
Rheumatoid factor (U/ml)	93.8 ± 105.5	158.7 ± 217.4	0.316
Matrix metalloproteinase-3 (ng/ml)	333.0 ± 249.1	328.1 ± 360.4	0.967
Disease activity score (DAS) 28-ESR	6.6 ± 1.4	6.4 ± 1.1	0.585
Dose of corticosteroid (mg/day)	2.3 ± 2.1	2.9 ± 3.2	0.583
Dose of methotrexate (mg/week)	7.6 ± 0.9	7.1 ± 1.1	0.202

Mean (±SD) values are shown. Unpaired Student's *t*-test was used to examine differences between the infliximab-discontinued group and the infliximab-continued group

completely suppressed in two of the patients tested (case 2, from 9 to 9; and case 4, from 30 to 30) for one year after the discontinuation.

Discussion

In this study, infliximab was administered to 172 active RA patients, despite receiving MTX for at least four weeks prior to infliximab. After we obtained continuous remission (DAS28 < 2.6), we tried to discontinue infliximab through the following strategic sequences. Depending on the level of disease activity, PSL and/or NSAIDs were initially reduced and discontinued, DMARDs other than MTX were stopped, and then, after clinical remission (DAS28-ESR < 2.6) had been maintained for more than 24 weeks, the discontinuation of infliximab was considered. Infliximab was successfully discontinued in nine patients with RA after we obtained informed consent from each patient. Clinical remission was maintained without recurrence in all nine RA patients, with only MTX 8 mg/w provided up to 29 months (mean of 14.2 months). Although there are no guidelines for the discontinuation of infliximab in RA patients in remission, our study indicates that DAS28-ESR could be a good indicator of whether to perform the strategic reduction of applied treatments.

Next, we compared the background characteristics of the group of nine patients who had successfully discontinued infliximab with those of another group who did not discontinue infliximab. Among multiple factors, the duration of disease was shorter and the points from Steinbrocker's stage-classification were significantly lower in the infliximab-discontinued group than in the infliximab-continued group. These findings imply that early intervention with infliximab appears to be advantageous for both achieving clinical remission and for discontinuing infliximab after clinical remission.

On the other hand, the biggest advantage of TNF blockade is the inhibition of bone destruction, as shown in multiple studies such as ASPIRE [8, 16]. However, there have been concerns over whether joint destruction can progress even after infliximab is discontinued. We

observed the complete inhibition of the progression of bone destruction, as measured by the modified Sharp score, for at least one year in two of these patients after infliximab was stopped.

Taken together, a treatment paradigm for RA in terms of the induction of remission and the suppression of joint destruction by TNF inhibitors such as infliximab has emerged. Once we have obtained clinical remission in patients treated with infliximab, the subsequent aim is the successful and safe discontinuation of infliximab, because of issues associated with cost and very long-term safety in relation to infection and malignancy. Our present study and the BeSt study indicate that DAS28-ESR could be a good indicator of whether the strategic reduction and/or discontinuation of concomitant treatment and infliximab can be performed, and whether, after infliximab has been discontinued, clinical remission and the suppression of joint destruction can be maintained with MTX alone, especially in early RA patients. However, further studies from multiple institutions are required to confirm these results and to promote a pivotal treatment strategy.

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