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ORIGINAL ARTICLE

Efficacy and safety of dose escalation of infliximab therapy in Japanese patients with psoriasis: Results of the SPREAD study

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ABSTRACT

Although infliximab is approved for psoriasis, its efficacy is reduced over time in some patients. The aim of this phase III trial is to evaluate efficacy and safety of infliximab dose escalation in Japanese psoriasis patients with loss of efficacy to standard-dose therapy. Patients with plaque psoriasis, psoriatic arthritis, pustular psoriasis or psoriatic erythroderma who showed loss of efficacy to standard-dose therapy received infliximab dose escalation (10 mg/kg every 8 weeks) from weeks 0 to 32. Loss of efficacy was defined as not maintaining 50% reduction in the Psoriasis Area and Severity Index (PASI 50) after achieving PASI 75. Efficacy and safety were evaluated up to week 40. Fifty-one patients received dose escalation and 43 completed the study. PASI 75 and median improvement rate of PASI score at week 40 were 44% and 70.0%, respectively, showing efficacy in skin symptoms. Efficacies in quality of life, nail psoriasis and joint pain were also obtained. Median serum infliximab level increased from less than 0.1 to 1.1 μg/mL from weeks 0 to 40, showing positive correlation between efficacy and serum infliximab level at week 40. Favorable efficacy was observed in patients with detectable serum infliximab levels (≥0.1 μg/mL) at baseline. Incidences of adverse events, serious adverse events, serious infections and serious infusion reactions were 92%, 10%, 4% and 0%, respectively. No marked difference was observed in both efficacy and safety among psoriasis types. No new safety concerns were observed. Infliximab dose escalation was effective and well-tolerated in psoriasis patients with loss of efficacy to standard-dose therapy, suggesting that dose escalation may be a useful therapeutic option for these patients.

Key words: **dose escalation, efficacy and safety, infliximab, Japanese, psoriasis.**

INTRODUCTION

Psoriasis is a chronic immune-mediated skin disease and its etiology is not fully elucidated.[1,2] Infliximab (IFX), a chimeric anti-tumor necrosis factor (TNF)-α antibody, is reported to be highly effective not only for plaque psoriasis, but also for psoriatic arthritis, pustular psoriasis and psoriatic erythroderma, the last two of which are considered more severe types.[3–10] In Western countries, IFX is approved for the treatment of psoriasis at a dose of 5 mg/kg every 8 weeks. However, the efficacy is reportedly reduced over time in some patients,[11,12] and dose adjustment has been recommended for such cases.[13,14] In fact, many patients who showed inadequate response to standard-dose treatment received a higher dose of IFX in clinical settings.[15,16]

In Japan, IFX has been approved since 2010 for the treatment of plaque psoriasis, psoriatic arthritis, pustular psoriasis

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and psoriatic erythroderma at 5 mg/kg in weeks 0, 2, 6 and 14, and every 8 weeks thereafter, and the efficacy and safety profiles of standard-dose IFX therapy in Japanese clinical settings was clarified.[17] However, loss of efficacy has been reported in some patients who had initially responded to standard-dose treatment[18] as observed in Western countries.

In order to evaluate the efficacy and safety of dose escalation of IFX therapy (10 mg/kg every 8 weeks) in Japanese psoriasis patients with loss of efficacy to standard-dose IFX maintenance therapy, the Study on Psoriasis Treatment with Remicade Escalating Dosage (SPREAD, NCT01680159) was conducted.

METHODS

The SPREAD study was a phase III, multicenter, single-arm, 40-week trial conducted at 34 sites in Japan. The study protocol was approved by the Ministry of Health and Labor as well as each institutional ethics committee, and the study itself was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice. Informed written consent was obtained from all patients.

Patients

Patients with plaque psoriasis, psoriatic arthritis, pustular psoriasis (except for localized pustular psoriasis) or psoriatic erythroderma, aged 16–75 years and showing loss of efficacy to standard-dose IFX originator (Remicade; Mitsubishi Tanabe Pharma, Osaka, Japan) therapy (5 mg/kg every 8 weeks), were included in the study. Patients with guttate psoriasis or drug-induced psoriasis were excluded. Loss of efficacy was defined as once achieving 75% reduction in the Psoriasis Area and Severity Index (PASI 75) response[19] continuously (judged by each investigator) to standard-dose IFX therapy, but then falling below PASI 50 at study entry (i.e. at initiation of dose escalation, week 0). PASI score at initiation of standard-dose IFX therapy (not at initiation of this study) was used as the baseline for evaluating PASI responses.

Patients with any of the following conditions were excluded from the study: a history of serious infusion reaction to standard-dose IFX therapy, active infection (including tuberculosis), active hepatitis B/C, other active skin diseases (e.g. allergic disease, skin infection), previous non-IFX biologic therapy, demyelinating disease, congestive heart failure, lymphoproliferative disease, lupus-like syndrome and pregnancy.

Study design

All patients who met the study criteria received IFX originator (Remicade) at 10 mg/kg every 8 weeks from weeks 0 to 32, and the efficacy and safety were evaluated until week 40. In patients who discontinued the study, the efficacy and safety were evaluated until 8 weeks after the last infusion. Prior to dose escalation, patients with plaque psoriasis or psoriatic arthritis received additional standard-dose IFX treatment to confirm that the loss of efficacy was not transient, and dose escalation of 10 mg/kg every 8 weeks was initiated (week 0) only in those who could not achieve PASI 50 response again after 8 weeks of additional treatment. For patients with pustular psoriasis or psoriatic erythroderma, dose escalation was initiated without additional treatment (week 0) if PASI response was less than 50%, given the severity of disease and due to ethical considerations.

Use of the following therapies was prohibited throughout the study period: immunosuppressants excluding methotrexate (MTX), phototherapy, injectable systemic corticosteroids, injectable-activated vitamin D3 derivatives, alkylating agents, lithium preparations, surgical operation, live vaccines and other investigational products. Use of MTX, etretinate, oral-activated vitamin D3 derivatives and oral corticosteroids was allowed provided the dose level was not increased during the study period (dose reduction was allowed). For patients with plaque psoriasis or psoriatic arthritis, dose change or initiation of new treatment was not allowed for 4 weeks (MTX, etretinate and oral-activated vitamin D3 derivatives) or 2 weeks (corticosteroids) prior to study entry.

Patients with a history of or suspected tuberculosis received prophylactic treatment with isonicotinic acid hydrazide (INH).

Efficacy

The primary end-point was PASI 75 response after dose escalation. The PASI score at initiation of standard-dose IFX therapy was used as the baseline for assessing PASI response. In addition, PASI 50/90 responses, global improvement (classified into four categories: resolved, improved, unchanged and worsened),[8] and Dermatology Life Quality Index (DLQI, 0–30 points)[20] were also assessed.

Physician's Global Assessment (PGA) (six grades: cleared, minimal, mild, moderate marked and severe)[9] was also assessed in patients with plaque psoriasis. The number of nails with psoriasis and Nail Psoriasis Severity Index (NAPSI, 0–8 points)[21] were assessed in patients with nail psoriasis; pain visual analog scale (VAS pain, 0–100 mm) was assessed in patients with psoriatic arthritis; and the degree of severity (mild, moderate or severe) was evaluated in patients with pustular psoriasis in accordance with the Japanese Dermatological Association's guidelines at 2010 (https://www.dermatol.or.jp/uploads/uploads/files/guideline/1372913421_3.pdf, Japanese article, last accessed 8 July 2016). All efficacies except DLQI and VAS pain were assessed by each investigator.

Laboratory tests

All laboratory tests were performed at LSI Medience (Tokyo, Japan). Serum IFX levels were measured via enzyme-linked immune sorbent assay (ELISA) using anti-IFX monoclonal antibodies obtained from Janssen Biotech (Horsham, PA, USA), with a lower detection limit of 0.1 μg/mL.[22] Serum anti-IFX antibodies (ATI) positivity were also evaluated via ELISA. In patients with detectable serum IFX levels (≥0.1 μg/mL), we considered these patients to be ATI-negative and did not evaluate ATI positivity (i.e. serum IFX levels were <0.1 μg/mL in all ATI-positive patients), as described previously.[22] Serum IFX level and ATI positivity were measured at Mitsubishi Tanabe Pharma (Osaka, Japan).

Statistical analyses

Efficacy and safety were analyzed in the full analysis set. The efficacy at each time point (weeks 0–40) was assessed using data as observed analysis. In addition, the last observation carried forward approach was also used in evaluating the efficacy at week 40. Statistical analyses were performed using SAS software version 9.2 (SAS Institute Japan, Tokyo, Japan).

RESULTS

Of the 62 patients who gave informed consent, 51 met the entry criteria and received IFX dose escalation (10 mg/kg every 8 weeks) from week 0. Of these 51 patients, 31 had plaque psoriasis, eight had psoriatic arthritis, seven had pustular psoriasis and five had psoriatic erythroderma. Patient characteristics for each psoriasis type are shown in Table 1. Characteristics did not differ markedly by psoriasis type. Median PASI score at initiation of standard-dose therapy (mean duration of 1.9 years prior to study) and at initiation of dose escalation (week 0) were 14.7 and 14.7, respectively; 41% of patients had a higher PASI score at week 0 than at initiation of standard-dose therapy. Eight patients discontinued the study, leaving 43 who ultimately completed the study (26 with plaque psoriasis, seven with psoriatic arthritis, five with pustular psoriasis and five with psoriatic erythroderma). Reasons for discontinuation were adverse events (AE) in six patients (including two with exacerbation of psoriasis) and withdrawal of consent in two patients (both had poor responses).

Efficacy in skin symptoms

Psoriasis Area and Severity Index 50/75/90 responses and global improvement rate (resolved or improved) over time in all patients are shown in Figure 1. PASI 75 responses ranged 40–64% after week 24, and 44% at week 40 (as observed). Global improvement rates ranged 88–95% at week 24 and thereafter, showing efficacy in most patients. Global improvement was assessed as worsened in only one patient with plaque psoriasis, and one with pustular psoriasis who dropped out of the study due to exacerbation of the disease. Among eight patients who discontinued the study, only one patient with plaque psoriasis achieved PASI 75 response at the discontinuation.

Median improvement rates of PASI score over time are listed for each psoriasis type in Table 2. Median value at week 40 was 70.0% in all patients and ranged 64.8–87.5%, depending on psoriasis type, with no marked differences among psoriasis types.

Quality of life improvement: DLQI score

Dermatological Life Quality Index was evaluated in all 51 patients. Mean DLQI scores were 8.3, 5.3, 4.6 and 3.9 at weeks 0, 8, 24 and 40, respectively, and DLQI remission rates (DLQI ≤1) were 14% (7/51) and 37% (16/43) at weeks 0 and 40, respectively, showing the improvement of patient

Table 1. Patient characteristics

		Type of psoriasis			
	All patients (n = 51)	Plaque psoriasis (n = 31)	Psoriatic arthritis (n = 8)	Pustular psoriasis (n = 7)	Psoriatic erythroderma (n = 5)
Male (%)	38 (75)	25 (81)	5 (63)	4 (57)	4 (80)
Age, years	49.5 (13.7)	51.2 (13.9)	50.1 (11.9)	36.7 (9.7)	55.8 (12.5)
Disease duration, years	19.8 (10.7)	18.7 (9.6)	20.1 (10.7)	22.9 (13.5)	21.8 (15.0)
Comorbidity (%)	47 (92)	28 (90)	8 (100)	7 (100)	4 (80)
History of psoriasis therapy (%)					
Systemic therapy	47 (92)	28 (90)	7 (88)	7 (100)	5 (100)
Phototherapy	38 (75)	22 (71)	6 (75)	6 (86)	4 (80)
Topical therapy	51 (100)	31 (100)	8 (100)	7 (100)	5 (100)
History of IFX therapy					
Duration, years	1.9 (1.1)	1.8 (0.8)	2.3 (1.9)	2.0 (1.0)	1.9 (0.8)
Dose just before this study, mg/kg	5.1 (5.0 to 5.7)	5.0 (4.9 to 5.7)	5.1 (5.0 to 5.5)	5.0 (5.0 to 5.7)	5.3 (5.2 to 6.0)
Interval just before this study, weeks	7.9 (7.0 to 8.0)	8.0 (7.0 to 8.0)	7.4 (7.1 to 7.9)	7.0 (6.0 to 7.4)	8.0 (8.0 to 8.0)
Body surface area, %	25 (11 to 44)	21 (11 to 37)	17 (5 to 45)	41 (34 to 61)	49 (20 to 52)
PASI at initiation of IFX standard-dose therapy	14.7 (10.3 to 25.0)	13.7 (10.3 to 19.5)	15.3 (5.0 to 25.9)	13.0 (9.7 to 27.6)	26.8 (25.0 to 32.3)
PASI at initiation of dose escalation (week 0)	14.7 (9.4 to 24.4)	12.8 (9.4 to 24.4)	14.0 (5.3 to 21.2)	14.7 (13.6 to 36.8)	22.2 (14.7 to 25.3)
DLQI	8.3 (7.7)	7.7 (8.2)	6.9 (4.5)	12.7 (7.4)	8.2 (8.8)
NAPSI†	3.9 (2.6)	3.8 (2.7)	2.5 (2.1)	5.0 (3.5)	4.4 (1.1)
Number of nail psoriasis†	6.7 (4.0)	6.4 (4.0)	5.7 (4.8)	7.2 (4.4)	8.6 (3.1)
Serum IFX level, μg/mL	<0.1 (<0.1 to 2.7)	<0.1 (<0.1 to 2.2)	<0.1 (<0.1 to 3.8)	<0.1 (<0.1 to 5.0)	1.4 (<0.1 to 2.4)

Data were number of patients (%), mean (standard deviation) or median (interquartile range). †n = 36. DLQI, Dermatology Life Quality Index; IFX, infliximab; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index.

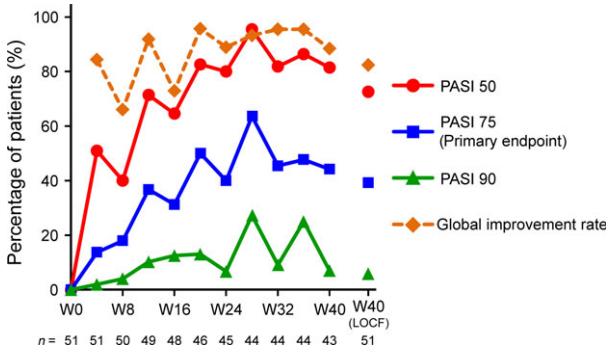

Figure 1. Reduction in Psoriasis Area and Severity Index of 50%, 75% and 90% (PASI 50/75/90) response and global improvement rate at week 0 to 40. Global improvement rate includes resolved and improved. Efficacy at each time point was evaluated using data as observed analysis, unless otherwise indicated. IFX, infliximab; W, week.

quality of life (QOL) by dose escalation (Table 3). In 27 patients with baseline DLQI of 5 or more (week 0), the proportion of patients with a DLQI improvement of 5 or more, which is considered as clinically meaningful improvement, at week 40 was 59% (13/22). The mean (standard deviation) change in DLQI at week 40 was −2.5 (5.2), −4.9 (3.4), −9.6 (7.2) and −5.6 (6.1) in patients with plaque psoriasis, psoriatic arthritis, pustular psoriasis and psoriatic erythroderma, respectively, showing that DLQI improved across all psoriasis types. Proportions of patients with successful treatment (defined as PASI 75 response or both PASI 50–<75 response and DLQI ≤5)[16] were 36% (18/50), 71% (32/45) and 77% (33/43) at weeks 8, 24 and 40, respectively. Of the eight patients withdrawn from the study, only two who discontinued due to AE had successful treatment at the time of discontinuation.

Efficacy in Physician Global Assessment

Physician Global Assessment was assessed in the 31 patients with plaque psoriasis (Table 3). The proportions of patients assessed as cleared, minimal, mild, moderate, marked and severe were 0%, 0%, 26%, 45%, 16% and 13% at week 0, and 8%, 38%, 35%, 15%, 4% and 0% at week 40, respectively, showing that skin symptoms of plaque psoriasis improved under the dose-escalation regimen.

Efficacy for nail psoriasis

Nail Psoriasis Severity Index and number of nails with psoriasis were assessed in the 36 patients with nail psoriasis at week 0 (Table 3). Mean NAPSI was 3.9, 3.4, 3.1 and 2.9 at weeks 0, 8, 24 and 40, respectively, showing that NAPSI tended to improve over time. Mean numbers of nails with psoriasis were 6.7, 6.0, 5.8 and 5.7 at weeks 0, 8, 24 and 40, respectively, similarly showing improvement with time. No marked differences were noted in improvement of nail psoriasis among psoriasis types (data not shown).

Efficacy for psoriatic arthritis

In patients with psoriatic arthritis (n = 8), mean VAS pain (0–100 mm) scores were 54.1, 47.8, 33.1 and 28.7 at weeks 0, 8, 24 and 40, respectively (Table 3), showing that joint pain improved under the dose-escalation regimen. Mean C-reactive protein (CRP) level at week 0 was 1.00 mg/dL (63% [5/8] were within normal range [≤0.5 mg/dL]), and was 0.46 mg/dL at week 40, without remarkable change.

Efficacy for generalized pustular psoriasis

Among patients with pustular psoriasis (n = 7), severity was mild in 71% (5/7) and moderate in 29% (2/7) at week 0 but mild in all until week 40 (Table 3). While improvements were noted for all skin symptoms (area of erythema, area of erythema with pustules and area of edema) and CRP levels, no

Table 2. Improvement rate of PASI score in each psoriasis type at weeks 0–40

	All patients (n = 43–51)	Plaque psoriasis (n = 26–31)	Psoriatic arthritis (n = 7–8)	Pustular psoriasis (n = 5–7)	Psoriatic erythroderma (n = 5)
Improvement rate of PASI score (%)					
Week 0	12.9 (−39.4 to 28.5)	14.4 (−56.2 to 28.5)	15.9 (−52.6 to 25.7)	−13.1 (−34.8 to 8.7)	31.3 (5.6 to 31.9)
Week 4	50.5 (28.9 to 65.7)	48.2 (26.2 to 63.6)	54.6 (31.8 to 67.0)	37.7 (23.9 to 56.4)	61.2 (57.4 to 83.2)
Week 8	44.1 (22.6 to 69.1)	41.7 (19.4 to 72.2)	44.8 (21.9 to 62.9)	66.4 (44.6 to 76.9)	47.8 (30.6 to 83.9)
Week 12	65.6 (47.5 to 81.7)	65.5 (52.3 to 81.7)	53.9 (16.7 to 65.7)	69.5 (47.5 to 82.3)	88.1 (67.6 to 89.5)
Week 16	62.1 (33.8 to 77.1)	63.5 (33.8 to 77.1)	43.7 (7.2 to 61.4)	62.5 (41.0 to 83.9)	64.2 (56.0 to 88.2)
Week 20	74.8 (59.5 to 84.6)	77.7 (65.4 to 85.1)	58.6 (46.4 to 74.6)	73.6 (59.5 to 83.9)	89.2 (76.4 to 89.5)
Week 24	73.2 (64.1 to 82.7)	72.9 (48.7 to 82.7)	74.6 (56.2 to 82.8)	68.6 (64.1 to 79.2)	74.1 (73.2 to 89.2)
Week 28	80.9 (69.0 to 90.9)	82.9 (68.0 to 91.2)	74.3 (63.2 to 81.5)	83.0 (77.2 to 87.7)	75.5 (65.4 to 93.8)
Week 32	72.9 (59.3 to 82.4)	72.1 (61.5 to 82.0)	74.6 (48.3 to 81.5)	75.6 (52.6 to 87.9)	80.8 (75.5 to 87.6)
Week 36	74.6 (64.3 to 87.4)	74.0 (62.4 to 84.0)	74.3 (61.8 to 93.4)	79.9 (72.2 to 82.6)	81.9 (80.8 to 92.6)
Week 40	70.0 (56.1 to 83.9)	64.8 (48.6 to 80.4)	69.0 (60.0 to 83.7)	82.6 (77.5 to 83.9)	87.5 (80.2 to 87.7)
Week 40 (LOCF)	67.5 (47.7 to 83.7)	64.4 (41.7 to 80.4)	65.4 (29.7 to 83.3)	77.5 (−10.4 to 83.9)	87.5 (80.2 to 87.7)

Data are median (interquartile range) percentage in improvement rate of PASI score. Efficacy at each time point was evaluated using data as observed analysis, unless otherwise indicated. LOCF, last observation carried forward; PASI, Psoriasis Area and Severity Index.

Table 3. Efficacies in DLQI, PGA, nail psoriasis, joint symptoms and pustular psoriasis

	Week 0	Week 8	Week 24	Week 40	Week 40 (LOCF)
Efficacy in QOL	(*n* = 51)	(*n* = 50)	(*n* = 45)	(*n* = 43)	(*n* = 51)
DLQI	8.3 (7.7)	5.3 (6.9)	4.6 (6.0)	3.9 (4.8)	5.1 (6.9)
DLQI ≤1 (%)	14	38	47	37	37
Efficacy in psoriasis vulgaris	(*n* = 31)	(*n* = 31)	(*n* = 27)	(*n* = 26)	(*n* = 31)
PGA					
Cleared/minimal/mild (%)	0/0/26	0/32/29	0/41/48	8/38/35	6/35/32
Moderate/marked/severe (%)	45/16/13	35/0/3	7/4/0	15/4/0	19/3/3
Efficacy in nail psoriasis	(*n* = 36)	(*n* = 35)	(*n* = 33)	(*n* = 31)	(*n* = 36)
NAPSI score	3.9 (2.6)	3.4 (2.6)	3.1 (2.6)	2.9 (2.7)	2.9 (2.8)
No. of nails with psoriasis	6.7 (4.0)	6.0 (4.4)	5.8 (4.6)	5.7 (4.3)	5.7 (4.3)
Efficacy in joint symptoms	(*n* = 8)	(*n* = 8)	(*n* = 7)	(*n* = 7)	(*n* = 8)
VAS pain, mm	54.1 (30.9)	47.8 (34.6)	33.1 (24.5)	28.7 (23.5)	28.5 (21.7)
Serum CRP, mg/dL	1.00 (1.47)	0.86 (1.69)†	–	0.46 (0.68)	0.45 (0.63)
Efficacy in pustular psoriasis	(*n* = 7)	(*n* = 6)	(*n* = 6)	(*n* = 5)	(*n* = 7)
Severity of pustular psoriasis					
Mild/moderate/severe (%)	71/29/0	83/17/0	100/0/0	100/0/0	100/0/0
Area of erythema	39.6 (22.8)	25.8 (25.6)	22.2 (19.2)	8.4 (8.5)	12.1 (9.5)
Area of erythema with pustules	5.4 (7.3)	1.7 (4.1)	0.3 (0.8)	0.0 (0.0)	1.4 (3.8)
Area of edema	4.1 (4.3)	1.7 (4.1)	0.3 (0.8)	0.0 (0.0)	1.0 (1.9)
Leukocyte count, /μL	8287 (3025)	7287 (1912)	7773 (1860)	7210 (830)	8321 (2323)
Serum CRP, mg/dL	2.21 (3.54)	1.93 (2.71)	1.00 (1.03)	0.24 (0.31)	0.51 (0.65)
Serum albumin, g/dL	3.91 (0.31)	3.82 (0.44)	4.05 (0.23)	4.16 (0.36)	4.07 (0.34)
Fever, °C	36.8 (0.4)	36.6 (0.5)	36.4 (0.3)	36.9 (0.3)	36.9 (0.3)

Data are mean (standard deviation) or percentage of patients. Efficacy at each time point was evaluated using data as observed analysis, unless otherwise indicated. †Week 16 (*n* = 8). CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; LOCF, last observation carried forward; NAPSI, Nail Psoriasis Severity Index; PGA, Physician Global Assessment; QOL, quality of life; VAS, visual analog scale.

marked changes were observed in any other laboratory parameters.

Correlation of trough serum IFX level with improvement of skin symptoms

Median (interquartile range) serum IFX trough levels were less than 0.1 (<0.1–2.7), less than 0.1 (<0.1–5.1), 0.9 (<0.1–5.2) and 1.1 μg/mL (<0.1–7.4) at weeks 0 (*n* = 51), 8 (*n* = 51), 24 (*n* = 45) and 40 (*n* = 44), respectively, showing that serum level was 1.0 μg/mL or more in 50% of patients at 40 weeks after the initiation of dose escalation. The proportion of patients with a serum IFX level below the lower detection limit (<0.1 μg/mL) was 59% (30/51) and 41% (18/44) at weeks 0 and 40, respectively.

Anti-IFX antibody prevalence was 29% (15/51) and 37% (19/51) at week 0 and during the study period (after dose escalation), showing that the prevalence did not increase markedly under the dose-escalation regimen.

A tendency was observed that PASI response was enhanced with increasing serum IFX level (Fig. 2). Patients with a serum IFX level of less than 1.0 μg/mL showed 67% response in PASI 50, but 19% in PASI 75 at week 40. In contrast, PASI 50/75 responses were 94% and 69% in patients with 1.0 to less than 10 μg/mL, and were 100% and 67% in patients with 10 μg/mL or more at week 40, showing similar response between these two patient groups.

Meanwhile, in patients with baseline (week 0) serum IFX level of less than 0.1 μg/mL (*n* = 30) or 0.1 μg/mL or more (*n* = 21), median improvement rates in PASI score were 41.7% and 63.8% at week 8, 69.8% and 74.3% at week 24, and 65.3% and 82.7% at week 40, respectively, showing that clinical efficacy tended to be greater in those with higher baseline serum IFX levels (Fig. 3).

Safety

The safety was evaluated up to week 40 for patients who completed the study and up to 8 weeks after the last dose of IFX

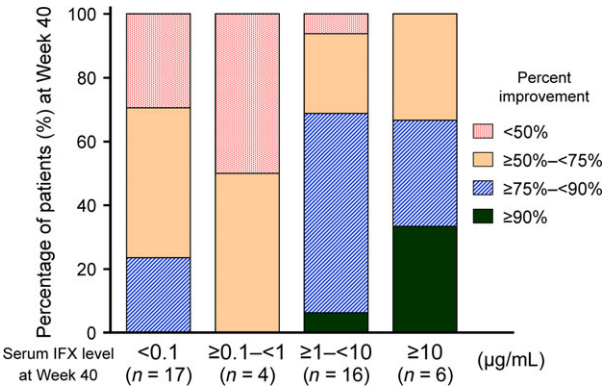

Figure 2. Clinical response at week 40 in patient groups stratified based on serum infliximab (IFX) levels at week 40. Efficacy was evaluated using data as observed analysis. PASI, Psoriasis Area and Severity Index.

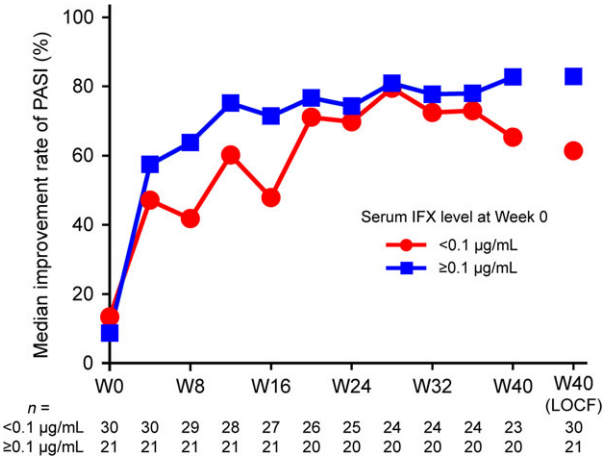

Figure 3. Clinical response in patients with detectable serum infliximab (IFX) level at the start of dose escalation (week 0). Efficacy at each time point was evaluated using data as observed analysis, unless otherwise indicated. LOCF, last observation carried forward; PASI, Psoriasis Area and Severity Index; W, week.

for those who dropped out. In all patients, the incidences of AE and serious AE (SAE) were 92% (47/51) and 10% (5/51), respectively (Table 4). Incidences of infections and serious infections were 43% (22/51) and 4% (2/51), respectively, with no cases of tuberculosis reported. The incidence of infusion reactions was 16% (8/51), with no serious ones reported. No deaths occurred. Six patients dropped out due to AE. However, among the six patients, one showed exacerbation of psoriasis during additional standard-dose treatment and then inadequate control after dose escalation; we therefore did not classify this patient has having an AE leading to discontinuation.

Common AE (classified by system organ class) were investigations (abnormal laboratory findings) (59%, 30/51), infections and infestations (45%, 23/51) and gastrointestinal disorders (27%, 14/51), showing that abnormal laboratory findings and infections were frequently reported. AE that occurred in at least 5% of patients were dsDNA antibody increased (49%, 25/51), nasopharyngitis (27%, 14/51), headache (8%, 4/51), urticaria (8%, 4/51), and cough, dyspnea and vomiting (6% each, 3/51).

Infusion reactions (defined as any AE occurring during or within 2 h after the completion of each infusion) occurred in 16% (8/51) patients; however, serious ones were not observed. Infusion reactions tended to correlate with ATI positivity or serum IFX level. Incidences of infusion reactions in ATI-positive patients (who showed ATI positivity at least once before or after dose escalation) and ATI-negative patients were 27% (6/22) and 7% (2/29), respectively, and those in patients with undetectable trough serum IFX level (<0.1 μg/mL) and detectable level (≥0.1 μg/mL) were 24% (6/25) and 8% (2/26), respectively, without significant differences. In contrast, no correlation of trough serum IFX levels with the other AE was observed (data not shown).

No marked differences were noted in the trend of AE among psoriasis types or any abnormal deviations from the previously reported safety profile. SAE reported in five patients were exacerbation of arthritis, cholecystitis, pyelonephritis, bacterial pneumonia, and colorectal cancer, the last three of which might have been caused by IFX.

DISCUSSION

While IFX is generally highly effective in treating autoimmune diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease, inadequate response has been reported in some patients.[23–26] In addition, many of these refractory patients were found to show low serum IFX trough levels, and serum IFX levels and efficacy elevated after dose escalation.[27–30] However, despite these promising findings, not many studies have examined the effect of IFX dose escalation on efficacy in the treatment of psoriasis, and its usefulness was unclear.[3,15] The aim of the SPREAD study was to evaluate the efficacy and safety of dose-escalating IFX therapy in psoriasis patients with loss of efficacy to standard-dose IFX therapy. Treatment at 10 mg/kg every 8 weeks not only increased serum IFX levels and alleviated skin symptoms but also improved patient QOL, nail psoriasis symptoms, pustular psoriasis symptoms and joint symptoms.

Table 4. Safety profile

		Type of psoriasis			
	All patients (n = 51) (%)	Plaque psoriasis (n = 31) (%)	Psoriatic arthritis (n = 8) (%)	Pustular psoriasis (n = 7) (%)	Psoriatic erythroderma (n = 5) (%)
Any AE	47 (92)	30 (97)	7 (88)	6 (86)	4 (80)
Serious AE	5 (10)	4 (13)	0	1 (14)	0
AE leading to discontinuation[†]	5 (10)	3 (10)	1 (13)	1 (14)	0
Any infections	22 (43)	13 (42)	1 (13)	5 (71)	3 (60)
Serious infections	2 (4)	2 (6)	0	0	0
Infusion reactions	8 (16)	7 (23)	0	1 (14)	0
Serious infusion reactions	0	0	0	0	0

[†]Not including one patients who showed exacerbation of psoriasis during additional 5 mg/kg treatment, and was not controlled adequately after dose escalation of infliximab. AE, adverse events. Data are number (%).

Although no marked change of CRP was observed in patients with psoriatic arthritis (Table 3), most patients showed normal level of CRP at the start of dose escalation (week 0); this may be the cause of no remarkable change.

Psoriasis Area and Severity Index 75 response at week 40 in this study was 44%, showing that efficacy was recovered in less than half of patients. The duration of loss of efficacy to standard-dose IFX therapy in the study participants is unknown. However, many patients might have shown loss of efficacy to standard-dose IFX therapy for a substantial period of time, given that the mean duration of IFX therapy prior to study entry was 1.9 years, the median PASI score at initiation of dose escalation (week 0) was similar to that at initiation of standard-dose therapy (median 14.7 at both time points, Table 1), and 59% of patients had a serum IFX level below the lower detection limit (<0.1 μg/mL) at week 0. In contrast, IFX was more effective in patients with a detectable IFX level (≥0.1 μg/mL) at initiation of dose escalation (week 0) than in those with an IFX level below the limit of detection (Fig. 3). These results suggest that dose escalation may be more effective if initiated early after loss of efficacy; that is, before the IFX trough level drops below the lower detection limit.

In addition to IFX dose escalation, switching to non-TNF biologics may be an option for patients with psoriasis refractory to standard-dose IFX therapy. However, phase III clinical studies in psoriatic arthritis showed that PASI 75 responses for the anti-interleukin (IL)-17 antibody secukinumab and anti-IL-12/23 antibody ustekinumab were 36–64% (week 24) and 36.1–50.0% (week 52), respectively, in patients previously treated with TNF inhibitors.[31,32] The efficacy of IFX at dose escalation may be comparable to that achieved with switching to other drugs, although differences in patient characteristics among studies preclude direct (or head-to-head) comparison.

Serum IFX levels markedly increased after dose escalation (median, <0.1 μg/mL at week 0 and 1.1 μg/mL at week 40) and correlated with clinical response (Fig. 2). Clinical studies in RA and Crohn's disease have shown that the threshold for clinical response to IFX is approximately 1.0 μg/mL.[27,33–37] In the present study, patients with serum IFX level of less than 1.0 μg/mL at week 40 had PASI 50/75 responses of 67% and 19%, respectively, which were substantially lower than those in patients with serum levels of 1.0 to less than 10 μg/mL and 10 μg/mL or more (PASI 50, 94% and 100%; PASI 75, 69% and 67%, respectively). In contrast, no marked differences were noted between patients with serum levels of 1.0 to less than 10 μg/mL and 10 μg/mL or more. However, because only four patients had a serum level of 0.1 or more to less than 1.0 μg/mL at week 40, the threshold for clinical response to IFX in psoriasis after dose escalation could not be accurately estimated in this study. Further clinical studies may be necessary to determine the threshold for clinical response.

Dose escalation of IFX showed good tolerability in this study. However, we could not clarify whether elevated serum IFX level by dose escalation resulted in increased AE or not, because serum IFX level in onset time of each AE was not evaluated. In contrast, the incidences of AE, SAE and infections in this study were similar to those reported in Japanese post-marketing surveillance of standard-dose of IFX therapy,[17] and the safety profiles were consistent with those in previous studies,[8,9] raising no new safety concerns. In addition, no correlation of trough serum IFX level with occurrence of AE was observed in this study. In consideration of these results, we think that dose escalation may not lead to increased AE.

Meanwhile, incidence of infusion reaction tended to be higher in patients with ATI-positive or undetectable trough serum IFX levels in our study. Although correlation of ATI or serum IFX level with infusion reactions was controversial,[38] careful attention should be paid in these patients, especially at the start of dose escalation.

Eight patients (16%) dropped out whose rate seemed to be slightly high. However, among eight patients, four were thought to discontinue this study probably due to non-response (two due to exacerbation of psoriasis, and two because of withdrawal of consent with poor responses). Therefore, we think that the drop-out rate in this study does not exceed that in previous studies.[8,9]

There are several limitations in the present study. First, this was a single-arm, open-label study and was not designed to determine the difference in efficacy between dose escalation and non-escalation. Second, the sample size of the study was relatively small. While neither efficacy nor safety differed markedly by psoriasis type, determining the difference in efficacy and safety among types was impossible, as less than 10 patients were affected either by psoriatic arthritis, pustular psoriasis or psoriatic erythroderma. Third, most efficacies were assessed by each investigator, which may cause some bias. Fourth, given the unknown duration of loss of efficacy, as mentioned above, no appropriate timing of IFX dose escalation could be determined.

Nevertheless, this study is the first clinical study to demonstrate the usefulness of IFX dose escalation in treating psoriasis patients with loss of efficacy to standard-dose IFX therapy, suggesting that IFX dose escalation may be a therapeutic option for these patients. Controlled clinical studies and cost-effectiveness analyses will be needed.

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