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Efficacy and safety of infliximab vs. methotrexate in patients with moderate-to-severe plaque psoriasis: results of an open-label, active-controlled, randomized trial (RESTORE1)

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Summary

Background Infliximab is indicated for treatment of moderate-to-severe plaque psoriasis in adults whose disease cannot be controlled with other systemic therapies, including methotrexate (MTX). To date, no studies have directly compared the efficacy and safety of infliximab and MTX.

Objectives To compare the efficacy and safety of infliximab vs. MTX in adults with moderate-to-severe plaque psoriasis.

Methods MTX-naïve patients (n = 868) were randomized 3 : 1 to receive infliximab 5 mg kg^{-1} at weeks 0, 2, 6, 14 and 22 or MTX 15 mg weekly with a dose increase to 20 mg weekly at week 6 if the Psoriasis Area and Severity Index (PASI) response was < 25%. At week 16, patients with < PASI 50 response could switch treatment groups. The primary efficacy endpoint was PASI 75 response at week 16. Major secondary efficacy endpoints were PASI 75 response at week 26, and the proportion of patients achieving a Physician's Global Assessment (PGA) score of cleared (0) or minimal (1) at weeks 16 and 26. Others included Dermatology Life Quality Index, 36-Item Short Form Health Survey, and PGA, PASI 50, PASI 75 and PASI 90 responses over time.

Results The primary endpoint was achieved by a significantly greater proportion of infliximab-treated patients (508/653, 78%) than MTX-treated patients (90/215, 42%; P < 0·001). Key secondary endpoints also were achieved by a greater proportion of infliximab-treated patients. Similar responses were observed at week 26 in patients who switched from MTX to infliximab at week 16. Overall adverse event (AE) incidence was comparable between groups, but incidence of serious and severe AEs was slightly higher in the infliximab group.

Conclusions Infliximab was well tolerated and more efficacious than MTX in patients with moderate-to-severe plaque psoriasis. Infliximab also was efficacious in patients who failed MTX and switched to infliximab.

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Conflicts of interest
See Appendix 1.

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Psoriasis is a chronic, inflammatory skin disease affecting more than 125 million people worldwide.[1–3] Plaque psoriasis occurs in about 80% of patients with psoriasis.[4,5] Typically, methotrexate (MTX) is prescribed for treatment of moderate-to-severe plaque psoriasis. MTX is associated with myelosuppression and hepatotoxicity, and clinical efficacy and optimal dosing regimens are uncertain due to limited data.[6]

The efficacy of infliximab, an IgG1 anti-tumour necrosis factor (TNF) monoclonal antibody for treatment of plaque psoriasis, has been assessed in three multicentre, randomized, double-blind, placebo-controlled trials.[7–9] The present open-label, active-controlled study is the first to make a direct comparison of the efficacy and safety of infliximab vs. MTX in adults with moderate-to-severe plaque psoriasis.

Patients and methods

Subjects

Study investigators enrolled eligible patients who were 18–75 years old with a diagnosis of moderate-to-severe plaque psoriasis for ≥ 6 months prior to screening, were candidates for phototherapy or systemic treatment, and had at least 10% of total body surface area affected and a Psoriasis Area and Severity Index (PASI) ≥ 12. Patients were excluded if they had received any previous treatment with MTX, or with a biologic or TNF antagonist within 3 months of baseline; had a diagnosis of congestive heart failure, history of chronic or recurrent infectious disease or serious infection, or had been hospitalized or received intravenous antibiotics for infection within the past 2 months; had had opportunistic infection within the past 6 months; had a history or signs/symptoms of lymphoproliferative disease; or had current or a history of malignancy. All patients were screened for tuberculosis. Systemic and topical treatments for psoriasis that could affect PASI evaluation were stopped 4 or 2 weeks, respectively, prior to starting study treatment. Institutional Review Board or Independent Ethics Committee approval and written informed consent were obtained before any study-related activity.

Study design

This phase IIIb open-label trial is registered in the U.S. National Institutes of Health clinicaltrials.gov database, identifier NCT00251641. It was initiated on 21 September 2005 and completed on 19 June 2008. The trial enrolment requirement was 800 randomized subjects. At each eligible subject's baseline visit, study centres telephoned the Interactive Voice Response System (IVRS; Quintiles, Morrisville, NC, U.S.A.) for randomization. IVRS assigned a patient randomization number. Patients were randomized 3 : 1 to receive infliximab 5 mg kg^{-1} (Remicade; Centocor BV, Leiden, the Netherlands) or MTX 2·5 mg tablets. Infliximab-treated patients received infusions at weeks 0, 2, 6, 14 and 22. MTX-treated patients received 15 mg weekly for the first 6 weeks; the dose could be increased at week 6 to 20 mg weekly in subjects with < 25% improvement in PASI from baseline. Use of folic acid was recommended but not mandated. Patients not achieving PASI 50 (≥ 50% improvement in PASI from baseline) at week 16 or who were intolerant to treatment could switch treatment groups. Subjects switching from MTX to infliximab received infliximab infusions at weeks 16, 18 and 22. Subjects switching from infliximab to MTX received MTX 15 mg weekly up to week 22 (Fig. 1). All patients had a follow-up visit at week 26.

Study endpoints

Patients were assessed for clinical response at all visits. All endpoints were determined *a priori*, as part of the study protocol before study execution. The primary efficacy endpoint was PASI 75 response (≥ 75% improvement in PASI from baseline) at week 16. Major secondary efficacy endpoints were the proportion of patients achieving PASI 75 at week 26 and a Physician's Global Assessment (PGA) score of cleared (0) or minimal (1) at weeks 16 and 26. Other secondary endpoints were the proportion of patients achieving PASI 50 and PASI 90 (≥ 90% improvement in PASI from baseline) at all visits; PASI 75 at weeks 2, 6, 10, 14, 18 and 22; mean change in PASI from baseline at all visits; median time to achieve PASI 75; mean change from baseline in Dermatology Life Quality Index (DLQI) at weeks 10, 16 and 26; and mean change from baseline in physical and mental component summary (PCS, MCS) scores of the 36-Item Short Form Health Survey (SF-36) at weeks 10, 16 and 26. British Association of Dermatologists guidelines define an adequate response to biologic therapy, as measured by the DLQI, as ≥ 5-point improvement within 3 months of treatment initiation.[10] Scores of 0 or 1 indicate that the disease is having no impact on the patient's quality of life (QoL).

Exploratory endpoints included the Rheumatoid Arthritis Disease Activity Index (RADAI), a self-administered questionnaire validated for rheumatoid arthritis (RA)[11] used to assess joint involvement in psoriasis, and the EuroQoL Health Questionnaire (EQ-5D), a nondisease-specific questionnaire used to describe health outcomes.[12] The RADAI was applied only to randomized subjects with psoriatic arthritis (PsA). Safety assessments were made at all visits.

Statistical analyses

Primary and secondary efficacy analyses were based on the intent-to-treat (ITT) population (n = 868). The ITT popula-

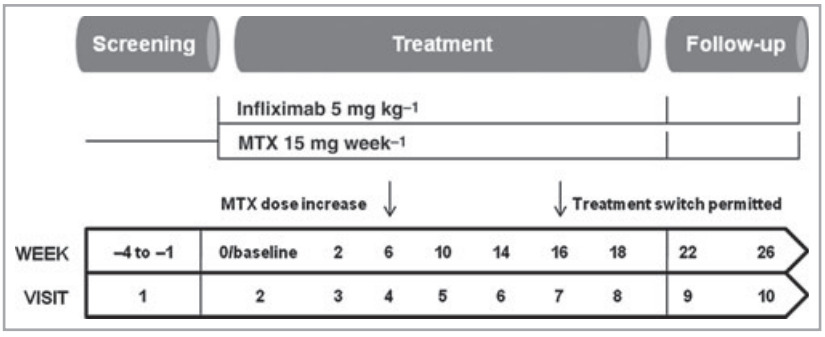

Fig 1. Study design. At week 6, methotrexate (MTX) dose was increased to 20 mg weekly in subjects with a Psoriasis Area and Severity Index (PASI) improvement from baseline < 25%. Patients not achieving PASI 50 (≥ 50% improvement in PASI from baseline) at week 16, or who were intolerant to treatment were permitted to switch treatment groups. Last treatments were week 22; follow-up visits occurred at week 26.

tion included all randomized patients: the data for four patients from each group who received no treatment were included in the intended treatment arm, and the data for one patient who was randomized to MTX but received infliximab was included in the infliximab arm. At week 16, patients who dropped out early or had missing data for PASI 75 and those who switched treatment were considered nonresponders. The proportion of patients achieving PASI 75 was compared between treatment groups using Pearson's χ^2 tests. Statistical tests were two sided and performed at α level 0·049. Two interim safety analyses were performed at α level 0·001: the first on 206 patients enrolled as of 19 June 2006 who had completed 16 weeks of treatment or had discontinued; the second on 262 subjects enrolled as of 5 December 2006 who had completed 16 weeks of treatment. Data for secondary efficacy endpoints were summarized by treatment group. Pearson's χ^2 test was used to compare treatment groups for the proportion of patients achieving PASI 50, PASI 75, PASI 90, and PGA score of cleared or minimal. Changes from baseline in PASI, DLQI, and PCS and MCS scores of the SF-36 were evaluated using the two-sample Wilcoxon Rank Sum test. A multiplicity adjustment for the major secondary endpoints (PASI 75 at week 26 and PGA score of cleared or minimal at weeks 16 and 26) was provided using the Hochberg test.

Confirmatory analysis of the primary endpoint was based on the efficacy-evaluable (per-protocol) population (n = 842; 635 infliximab, 207 MTX), which included all patients who met key eligibility and evaluability criteria. Patients who were randomized but never received study treatment, or had unacceptable baseline criteria (baseline PASI ≤ 10), incomplete efficacy data, or unacceptable concomitant medication were excluded from this dataset.

Safety analyses were based on the dataset comprising all randomized patients who received at least one dose of study medication. Safety data are reported both prior to and after treatment switch at week 16. Serious adverse events (SAEs) were designated severe at investigator discretion.

Results

Patient population

In total, 868 patients at 106 European centres were randomized to receive infliximab 5 mg kg^{-1} (n = 653) or MTX (n = 215). Demographic and baseline characteristics were well balanced across treatment groups (Table 1). A similar proportion of patients in each group had received previous systemic treatment; only 8% of patients in either group had received previous biologic treatment (Table 2). Three patients in the infliximab group and 84 patients in the MTX group received folic acid supplementation.

Eighty-three per cent of patients randomized to infliximab and 59% randomized to MTX completed the treatment to which they were originally assigned. More patients in the MTX group (88/215, 41%) discontinued therapy compared with the infliximab group (112/653, 17%). This disparity is due primarily to the large number of MTX patients (63/215, 29%) who switched to infliximab (MTX-to-IFX) at week 16. Only 1% of patients (9/653) initially randomized to infliximab switched to MTX (IFX-to-MTX) at week 16 (Fig. 2). At week 6, the MTX dose could be increased to 20 mg weekly if PASI 25 was not achieved; 25% (54/215) of patients received a dose of 20 mg for at least one visit between weeks 6 and 16.

Efficacy

Significantly more infliximab patients (508/653, 78%) than MTX patients (90/215, 42%) achieved PASI 75 at week 16

Table 1 Patient baseline characteristics

Characteristics	Infliximab (n = 653)	MTX (n = 215)
Gender, male, n (%)	438 (67)	148 (69)
Race, caucasian, n (%)	636 (97)	211 (98)
Age (years), mean (range)	44·1 (18–78)	41·9 (18–69)
Weight (kg), mean ± SD	84·5 ± 18·6	83·8 ± 18·2
Body mass index (kg m^{-2}), mean ± SD	28·0 ± 5·8	27·7 ± 5·0
Years since diagnosis, mean ± SD	18·8 ± 11·6	17·0 ± 10·3
BSA (%), mean ± SD n = 650 infliximab, 215 MTX	31·9 ± 16·5	31·0 ± 15·0
PASI, mean ± SD n = 650 infliximab, 215 MTX	21·4 ± 8·0	21·1 ± 7·6
DLQI, mean ± SD n = 639 infliximab, 207 MTX	13·5 ± 7·2	13·8 ± 7·6
RADAI score[a], mean ± SD n = 118 infliximab, 36 MTX	3·62 ± 2·23	3·52 ± 2·02

MTX, methotrexate; BSA, body surface area; PASI, Psoriasis Area and Severity Index; DLQI, Dermatology Life Quality Index; RADAI, Rheumatoid Arthritis Disease Activity Index. [a]The RADAI was applied only to the 154 subjects with psoriatic arthritis.

History n (%)	Infliximab (n = 653)	MTX (n = 215)
All systemic and biologic treatments	407 (62·3)	142 (66·0)
All nonbiologic systemic treatments	399 (61·1)	139 (64·7)
PUVA/psoralens for topical use/methoxsalen	187 (28·6)	60 (27·9)
Ciclosporin	81 (12·4)	34 (15·8)
Acitretin/etretinate	148 (22·7)	58 (27·0)
Fumaric acid/fumaric acid esters/Fumaderm	151 (23·1)	57 (26·5)
Leflunomide	2 (0·3)	0
Mycophenolate mofetil/mycophenolic acid	0	1 (0·5)
All biologic treatments	54 (8·3)	18 (8·4)
Alefacept	12 (1·8)	5 (2·3)
Efalizumab	18 (2·8)	6 (2·8)
Etanercept	26 (4·0)	9 (4·2)
Investigational drugs	2 (0·3)	2 (0·9)

MTX, methotrexate; PUVA, psoralen plus ultraviolet A.

Table 2 Patient history of systemic and biologic treatments

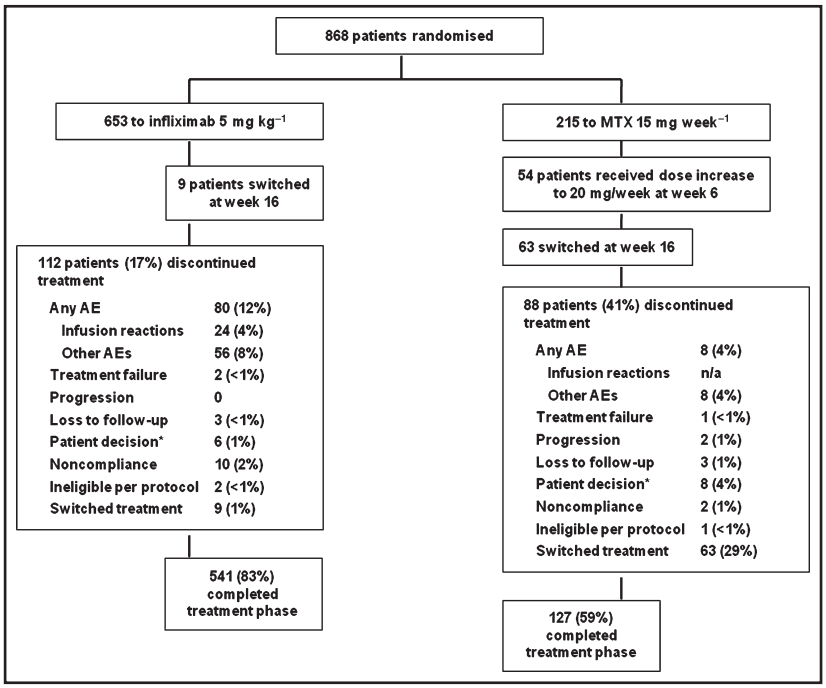

Fig 2. Patient disposition. At week 6, the methotrexate (MTX) dose was increased to 20 mg weekly in patients with a Psoriasis Area and Severity Index (PASI) change from baseline < 25%. At week 16, patients with < 50% improvement in PASI from weeks 0–16 were allowed to switch treatment groups. Subjects who dropped out or switched treatment were considered PASI nonresponders. AE, adverse event; n/a, not applicable. *Subjects did not wish to continue, and their decision was unrelated to treatment.

(P < 0·001; Fig. 3). A difference between groups in the proportion of subjects achieving PASI 75 was observed as early as week 2 and was maintained throughout the 26-week study. At week 26, 77% (502/653) of patients receiving infliximab and 31% (66/215) receiving MTX achieved PASI 75 (P < 0·001). Subjects who dropped out or switched treatment at week 16 were considered PASI nonresponders at week 26. Median time to achieve PASI 75 was shorter in the infliximab group (46 days, 95% confidence interval [CI] 45–50) vs. the MTX group (127 days, 95% CI 113–154; P < 0·0001).

The proportion of patients achieving PASI 50 and PASI 75 was significantly higher in the infliximab group than the MTX group at all visits (P < 0·001; Table 3). The proportion of patients achieving PASI 90 was significantly higher (P < 0·001) in the infliximab group at all visits except week 2 (P = 0·055; Fig. 4).

Of MTX-to-IFX patients (n = 63), 73% (46/63) achieved PASI 75 at week 26, compared with 11% (1/9) of IFX-to-MTX patients (n = 9; Fig. 5). At weeks 18 and 22, 23% and 60% of MTX-to-IFX patients achieved PASI 75 response, compared with 0% and 11% of IFX-to-MTX patients. No IFX-to-MTX patients achieved PASI 90 response at any visit after week 16, compared with 48% of MTX-to-IFX patients.

The mean change from baseline in PASI was significantly greater in the infliximab group vs. the MTX group at all visits (P < 0·001). The mean PASI decreased from 21·4 at baseline to 3·5 at study endpoint in the infliximab group—a reduction of 83%. The reduction was 54% in the MTX

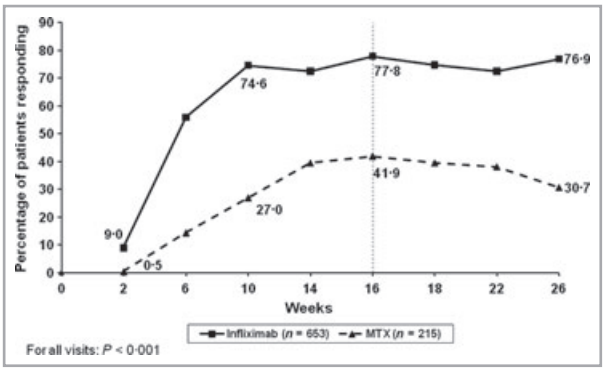

Fig 3. PASI 75 response by visit (intent-to-treat population). Patients achieving < PASI 50 by week 16 (grey line) were permitted to switch treatment groups. MTX, methotrexate.

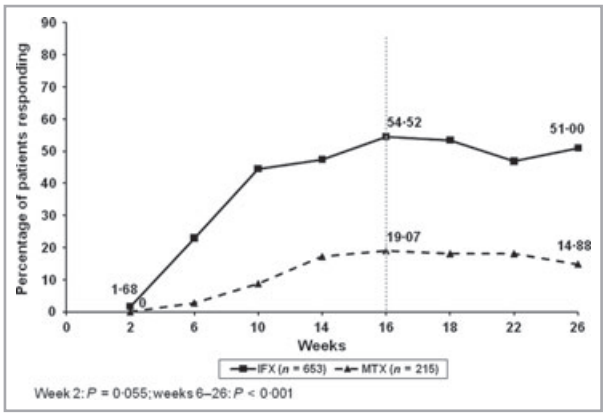

Fig 4. PASI 90 response by visit (intent-to-treat population). Patients achieving < PASI 50 by week 16 (grey line) were permitted to switch treatment groups. IFX, infliximab; MTX, methotrexate.

group, with a decrease from 21·1 at baseline to 9·7 at study endpoint.

At weeks 16 and 26, the proportion of patients who achieved a PGA score of cleared or minimal was significantly greater in the infliximab group (76% and 73%, weeks 16 and 26, respectively) vs. the MTX group (38% and 28%, weeks 16 and 26, respectively; all comparisons P < 0·001). The proportion of patients who achieved a PGA score of cleared or minimal after switching treatment was greater in the MTX-to-IFX

Table 3 PASI 50, 75 and 90 response rates by visit

	Infliximab (n = 653[a])			MTX (n = 215[a])		
Visit	Responded, n (%)	Switched, n	Dropped out, n	Responded, n (%)	Switched, n	Dropped out, n
PASI 50						
Week 2	247 (37·8)	n/a	7	19 (8·8)	n/a	4
Week 6	535 (81·9)	n/a	19	80 (37·2)	n/a	5
Week 10	579 (88·7)	n/a	29	118 (54·9)	n/a	9
Week 14	562 (86·1)	n/a	44	131 (60·9)	n/a	12
Week 16	567 (86·8)	9	58	130 (60·5)	63	13
Week 18	543 (83·2)	9	69	120 (55·8)	63	21
Week 22	530 (81·2)	9	75	118 (54·9)	63	24
Week 26	529 (81·0)	9	94	103 (47·9)	63	25
PASI 75						
Week 2	59 (9·0)	n/a	7	1 (0·5)	n/a	4
Week 6	365 (55·9)	n/a	19	31 (14·4)	n/a	5
Week 10	487 (74·6)	n/a	29	58 (27·0)	n/a	9
Week 14	473 (72·4)	n/a	44	85 (39·5)	n/a	12
Week 16	508 (77·8)	9	58	90 (41·9)	63	13
Week 18	488 (74·7)	9	69	85 (39·5)	63	21
Week 22	473 (72·4)	9	75	82 (38·1)	63	24
Week 26	502 (76·9)	9	94	66 (30·7)	63	25
PASI 90[b]						
Week 2	11 (1·7)	n/a	7	0	n/a	4
Week 6	150 (23·0)	n/a	19	6 (2·8)	n/a	5
Week 10	291 (44·6)	n/a	29	19 (8·8)	n/a	9
Week 14	310 (47·5)	n/a	44	37 (17·2)	n/a	12
Week 16	356 (54·5)	9	58	41 (19·1)	63	13
Week 18	349 (53·4)	9	69	39 (18·1)	63	21
Week 22	306 (46·9)	9	75	39 (18·1)	63	24
Week 26	333 (51·0)	9	94	32 (14·9)	63	25

MTX, methotrexate; n/a, not applicable. [a]All randomized subjects. [b]P < 0·001 all visits except week 2 (P = 0·055). Note: subjects who dropped out or switched treatment at week 16 were considered PASI nonresponders at all subsequent visits.

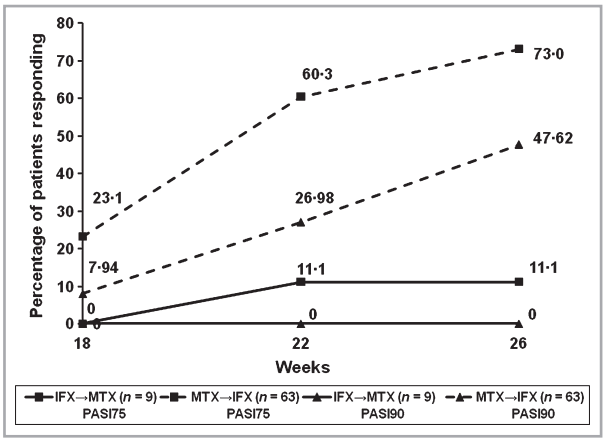

Fig 5. PASI 75 and PASI 90 response rates by visit for patients who switched treatment at week 16. Response rates are based on the improvement from week 16 in Psoriasis Area and Severity Index (PASI). Subjects who dropped out or switched treatment at week 16 were considered PASI nonresponders at all subsequent visits. IFX, infliximab; MTX, methotrexate.

group than the IFX-to-MTX group at week 18 (30% vs. 0%, respectively), week 22 (71% vs. 11%, respectively) and week 26 (75% vs. 22%, respectively).

Improvement in health-related (HR) QoL was greater in the infliximab group vs. the MTX group as measured by the DLQI, SF-36 and EQ-5D metrics. At weeks 10, 16 and 26, the mean change from baseline in the DLQI total score was significantly greater in those receiving infliximab (week 10: −11·4 vs. −7·90, $P < 0·001$; week 16: −11·6 vs. −8·95, $P < 0·001$; week 26: −11·3 vs. −9·14, $P = 0·004$; Fig. 6). At week 16, 64% (353/550) of infliximab patients had a DLQI score of 0 or 1, compared with 37% (69/186) of MTX patients; 83% (453/544) of infliximab patients and 67% (124/185) of MTX patients had a ≥ 5-point DLQI reduction from baseline.

Mean improvements from baseline of the PCS and MCS scores (SF-36) were greater in the infliximab group vs. the MTX group at all timepoints. At weeks 10 and 16, the change in the mean PCS score was significantly greater in the infliximab group (week 10: 5·15 vs. 3·00, $P < 0·001$; week 16: 5·53 vs. 3·76, $P < 0·002$), and the same was true for the mean MCS score at week 10 (7·94 vs. 5·63, $P \leq 0·041$).

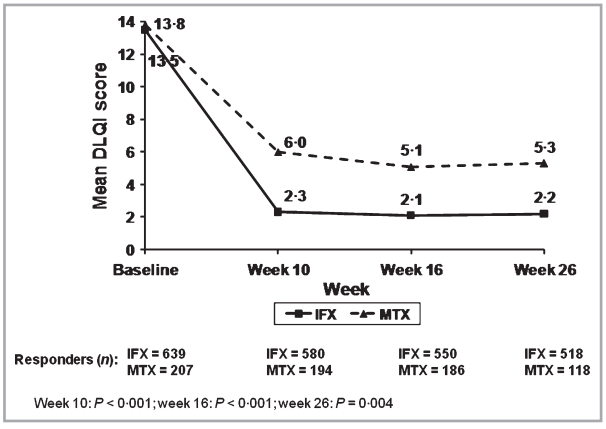

Fig 6. Mean total Dermatology Life Quality Index (DLQI) scores by visit. Subjects who dropped out or switched treatment at week 16 were considered nonresponders at all subsequent visits. IFX, infliximab; MTX, methotrexate.

Quality of life and Rheumatoid Arthritis Disease Activity Index

Mean composite EQ-5D scores were consistently higher in the infliximab group vs. the MTX group ($P < 0·05$) at weeks 10 (0·86 vs. 0·81), 16 (0·86 vs. 0·84) and 26 (0·86 vs. 0·81).

The RADAI analysis was performed in patients with PsA (n = 154)—infliximab n = 118, 18%; MTX n = 36, 16·7%. The mean composite RADAI scores were consistently lower in the infliximab group at weeks 10 (2·32 vs. 2·95), 16 (2·16 vs. 2·80) and 26 (2·0 vs. 2·98). Each component score also was consistently lower in the infliximab group.

Safety

Incidence of adverse events (AEs) was comparable between treatment groups for the week-16 and week-26 datasets (Table 4). A substantial proportion of MTX patients (29%) crossed over to infliximab at week 16. Therefore, the incidence of AEs was evaluated using three different datasets: (i) all AEs reported up to week 16; (ii) all AEs reported up to week 26, excluding AEs reported after week 16 for patients who switched; and (iii) all AEs following treatment switch. Comparisons of AE incidence should be conducted with caution due to the open-label design of the study and differences in study medication exposure that resulted from treatment switch at week 16.

Up to week 16, 64% of infliximab patients and 63% of MTX patients experienced at least one AE. In the MTX group, the most common treatment-related (tr) AEs up to week 16 were nasopharyngitis (5%), fatigue (8%), headache (7%) and nausea (7%). In the infliximab group, the most common trAEs up to week 16 were infusion-related reactions (9%), nasopharyngitis (6%) and headache (5%). Infusion-related reactions were mild in 3% (21/649), moderate in 5% (34/649) and severe in 3% (19/649) of patients. See Table 4 for the most common trAEs up to week 26.

A similar proportion of patients in each group experienced a serious infection. Up to week 16, the proportion of subjects reporting at least one SAE was 6% (36/649) in the infliximab group and 2% (4/211) in the MTX group. Severe/life-threatening SAEs up to week 16 were experienced by 5% (30/649) of infliximab subjects and < 1% (1/211) of MTX subjects. The most common SAE was infusion-related reaction, reported for 1% (8/649) of infliximab patients up to week 16. All of these serious reactions were severe. All other individual SAEs occurred in < 1% of subjects in each group.

SAE incidence increased slightly up to week 26 (44/649 [7%] of IFX subjects and 6/211 [3%]) of MTX subjects. The proportion of subjects with severe/life-threatening SAEs up to

Table 4 Adverse events (AEs) up to week 26[a] (excluding those beginning on or after treatment switch)

Adverse Event, n (%)	Infliximab (n = 649)	MTX (n = 211)
Patients reporting any AE	466 (72)	142 (67)
Patients reporting treatment-related AEs	309 (48)	94 (45)
Most common treatment-related AEs		
Abdominal pain	3 (< 1)	6 (3)
Abdominal pain, upper	3 (< 1)	7 (3)
Diarrhoea	10 (2)	12 (6)
Nausea	11 (2)	16 (8)
Fatigue	22 (3)	16 (8)
Infusion-related reaction	70 (11)	0
Nasopharyngitis	60 (9)	16 (8)
Headache	36 (6)	17 (8)
Pruritus	19 (3)	3 (1)
Serious AEs, overall	44 (7)	6 (3)
Serious infections[b]	10 (2)[c]	4 (2)
Infusion-related reactions (all severe)	17 (3)	0
Lymphoproliferative disorders and malignancies	1 (< 1)[d]	0
Patient discontinuations due to AEs	81 (12)	9 (4)
Liver test abnormalities	14 (2)	3 (1)

MTX, methotrexate. [a]Exposure to the initially assigned study medication differed in the week-26 dataset. [b]Prespecified categories: tuberculosis; opportunistic infections such as *Pneumocystis jiroveci* (formerly *P. carinii*) pneumonia, listeriosis, atypical mycobacteria, histoplasmosis, salmonellosis and serious viral infections. [c]Lyme disease, pharyngitis (not severe); tuberculosis, two cases of pneumonia, viral infection (severe). [d]Basal cell carcinoma.

week 26 increased slightly in the IFX group (35/649, 5%) and decreased slightly in the MTX group (3/211, 1%). Other than the SAEs of interest described for the week-16 dataset, no additional noteworthy SAEs occurred up to week 26. No additional serious infusion-related events occurred.

Up to week 26, 12% of infliximab patients and 4% of MTX patients discontinued treatment due to AEs. Liver function test (LFT) abnormalities led to the discontinuation of study medication in 2% (14/649) of infliximab patients and 1% (3/211) of MTX patients. LFT abnormalities were severe in five of the 14 infliximab patients and one of the three MTX patients. The most common reason for discontinuation of infliximab was infusion-related reaction (24/649, 4%).

Following treatment switch at week 16, no trAEs were reported up to week 26 for the nine IFX-to-MTX patients. trAEs were reported for 16 of the 63 MTX-to-IFX patients (25%); two of these AEs were severe. One patient experienced psoriatic arthropathy, and the other discontinued study medication due to bacterial arthritis and staphylococcal infection. The most common trAE in patients who switched was infusion-related reaction (5/63, 8%).

Discussion

RESTORE1 demonstrates greater efficacy of infliximab compared with MTX in both skin and HRQoL measures in MTX-naïve patients with moderate-to-severe plaque psoriasis. Infliximab was significantly more effective in achieving PASI 75 and PGA score of cleared or minimal at weeks 16 and 26. A greater proportion of infliximab patients achieved most secondary endpoints, including PASI 50 and PASI 90 response. At baseline, the mean composite RADAI score and each component score were comparable between treatment groups; however, at each follow-up visit the scores were consistently lower in the infliximab group.

Due to the open-label design of our study, efficacy in the infliximab group may have been overestimated compared with the MTX group. Nevertheless, our study does confirm efficacy results of three double-blinded trials of infliximab vs. placebo: SPIRIT, EXPRESS and EXPRESS II.[7–9] In these studies at week 10, over 70% of infliximab patients had achieved PASI 75, compared with about 5% of placebo patients. Efficacy was maintained over 52 weeks, and infliximab was generally well tolerated. HRQoL, as assessed by the DLQI, was significantly improved in infliximab patients compared with placebo-treated patients.[7,9,13] This is important because plaque psoriasis has been linked to depression and suicidal tendencies.[14]

Despite extensive use of MTX as systemic therapy for psoriasis, the number of high-quality controlled trials is limited. Of three trials of MTX monotherapy in psoriasis, only one fulfilled criteria for inclusion in the European S3-Guidelines,[6] used PASI, and included current methodological standards. This 16-week randomized, controlled trial investigated efficacy of MTX monotherapy in patients (n = 85) with moderate-to-severe plaque psoriasis.[15] At week 16, 60% (26/43) of

MTX patients achieved PASI 75 and 40% (17/43) achieved PASI 90, compared with 71% (P = 0·29) and 33% (P = 0·55) of ciclosporin-treated patients, respectively. Twelve patients discontinued MTX because of elevated liver enzymes.[15]

In our significantly larger study at week 16, 42% (90/215) of MTX patients achieved PASI 75, and 19% (41/215) achieved PASI 90. The difference in MTX response rate between our study and the study of Heydendael *et al.* might be explained by lower disease activity in the latter: the MTX group had a mean PASI of 13·4 at baseline, and only three subjects had PsA. In our study, the MTX group had a mean PASI of 21·1 at baseline, and 36 subjects had PsA.

The Comparative Study of Humira vs. Methotrexate vs. Placebo in Psoriasis Patients (CHAMPION) trial examined MTX vs. adalimumab.[16] Subjects (n = 271) had long-term plaque psoriasis (mean 18·5 years) and were naïve to both TNF inhibitors and MTX. In this 16-week randomized, double-blind, placebo-controlled trial, the starting MTX dose was 7·5 mg weekly to avoid the high drop-out rate due to elevated liver enzymes observed by Heydendael *et al.*[15] Despite the different dosing regimens and other dissimilarities between the CHAMPION and RESTORE1 trials, it is interesting to compare the efficacy of MTX: 36% (40/110) of MTX subjects achieved PASI 75 in the former, compared with 42% (90/215) in our study. Also, our higher starting dose of 15 mg weekly did not result in a higher drop-out rate due to AEs, which was below 5% and comparable with the CHAMPION drop-out rate.[16] The clinical efficacy of MTX and the optimal dosing regimen in plaque psoriasis continue to be debated.[6]

In RESTORE1, infliximab appears to be more effective than MTX not only in MTX-naïve subjects but also in subjects who failed to respond to initial treatment with MTX at week 16. Patients randomized to MTX and remaining on MTX up to week 16 showed a slow decline in response up to week 26. However, MTX data after week 16 must be interpreted with caution because the MTX population was small, and MTX was stopped at week 22.

Infliximab and MTX were generally well tolerated. The incidence and type of AEs were comparable between treatment groups, and most AEs were mild or moderate in severity. However, more infliximab patients discontinued due to AEs. SAE incidence was slightly greater in the infliximab group. Except for the occurrence of infusion reactions, the greater incidence of SAEs was not due to more AEs in any specific body system/organ class, but rather to more individual AEs, each occurring in < 1% of subjects, across all body system/organ classes. Incidence of severe SAEs also was slightly greater in the infliximab group. The rate of infusion-related reactions (9% up to 16 weeks, 11% up to 26 weeks) was similar to that reported in other studies[9] of infliximab in moderate-to-severe psoriasis. Differences in AE incidence between the groups are numerical, because a detailed statistical analysis was not performed.

The trial's crossover design produced an imbalance in study medication exposure, possibly affecting reported AE incidences. Adjusting AEs for exposure to study medications (per 100 person-years [PY] of follow-up) was comparable between groups (152 PY and 158 PY, respectively). The open-label design may have led to bias in reporting of specific AEs, especially in their classification as serious, in favour of MTX. Heightened safety concerns regarding infusion-related reactions, infections and LFT abnormalities for subjects receiving infliximab may have led to more hospitalizations or a more severe classification of AEs than for subjects receiving MTX.

Use of RADAI as an exploratory endpoint has some limitations, because it is validated for RA, but not PsA. However, as RESTORE1 was conducted by dermatologists, collecting this 'real-world' patient experience was deemed important. The mean composite RADAI scores were consistently lower in the infliximab group vs. the MTX group, suggesting lower arthritic disease activity in the former.

In conclusion, infliximab was significantly more effective than MTX in achieving PASI 75 response and PGA score of cleared or minimal in patients with moderate-to-severe plaque psoriasis. Improvements in QoL were consistently greater in the infliximab group vs. the MTX group, as confirmed by DLQI, SF-36 and EQ-5D analyses. The time to PASI 75 response was significantly shorter, and a trend toward improved psoriatic joint involvement was observed. As this is the first study to make a direct comparison of infliximab and MTX in the treatment of moderate-to-severe plaque psoriasis, additional blinded studies of longer duration should be executed to confirm these results.

What's already known about this topic?

- To date, no studies have directly compared the efficacy and safety of infliximab and methotrexate (MTX).
- Efficacy and safety of infliximab vs. placebo have been shown in three double-blinded trials.[7,8,9]
- The number of high-quality controlled trials of MTX as systemic therapy for psoriasis is limited.
- Of three trials of MTX monotherapy in psoriasis, only one[15] fulfilled criteria for inclusion in the European S3-Guidelines,[6] used Psoriasis Area and Severity Index, and included current methodological standards.
- MTX and adalimumab were compared in the CHAMPION trial.[16]

What does this study add?

- The RESTORE1 study is the first to make a direct comparison of the efficacy and safety of infliximab and MTX.
- This study confirms the efficacy and safety results of three double-blinded trials of infliximab vs. placebo.[7,8,9]
- The RESTORE1 trial is significantly larger than the MTX monotherapy trial[15] mentioned above.

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Appendix 1. Conflicts of interest

J.B. has served as a consultant and/or paid speaker for, and/or participated in clinical trials sponsored by companies that manufacture drugs used for the treatment of psoriasis including Abbott, Celgene, Centocor, Janssen-Cilag, Johnson and Johnson, Merck, Novartis, Pfizer, Schering-Plough and Wyeth. M.H. has served as a consultant and/or paid speaker for, and/or has participated in clinical trials sponsored by Abbott, Amgen, Essex, Janssen, Leo, Medac, Novartis, Pfizer, Schering-Plough and Wyeth. G.W. has no conflicts of interest to disclose. J.-P.O. has been a consultant for Schering-Plough, Abbott, Merck-Serono, Centocor, Wyeth, Janssen-Cilag, Meda-Pharma, Pierre-Fabre and Galderma. H.Z. is an employee of Merck, Sharp & Dohme. H.v.H. was an employee of Merck, Sharp & Dohme at the time of the RESTORE1 study and during the preparation of this manuscript. K.R. has served as a consultant and/or paid speaker for, and/or participated in clinical trials sponsored by Abbott, Celgene, Centocor, Janssen-Cilag, Leo, Medac and Merck.