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Infliximab Inhibits Progression of Radiographic Damage in Patients With Active Psoriatic Arthritis Through One Year of Treatment

Results From the Induction and Maintenance Psoriatic Arthritis Clinical Trial 2

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Objective. **To evaluate the effect of infliximab on progression of structural damage over 1 year in patients with active psoriatic arthritis (PsA) enrolled in the Induction and Maintenance Psoriatic Arthritis Clinical Trial 2.**

Methods. **In this double-blind, placebo-controlled study, 200 patients with active PsA were randomly assigned (1:1 ratio) to receive infusions of infliximab (5 mg/kg) or placebo at weeks 0, 2, and 6, and every 8 weeks thereafter through week 54. At week 24, patients initially assigned to receive placebo crossed over to receive infliximab (5 mg/kg). Based on predefined criteria, patients randomized to receive placebo could enter early escape by receiving infliximab (5 mg/kg) starting at week 16, and patients randomized to receive infliximab could have the dose increased to 10 mg/kg starting at week 38. Patients were analyzed according to the treatment they were randomized to receive. Radiographs of hands and feet were obtained at baseline and at weeks 24 and 54. Two readers blinded to treatment assignment and radiograph sequence independently evaluated erosions and joint space narrowing using the Sharp/van der Heijde scoring method modified for PsA.**

Results. **At week 24, patients randomized to receive infliximab 5 mg/kg had significantly less radiographic progression compared with patients randomized to receive placebo, with mean ± SD changes from baseline in the total Sharp/van der Heijde score of −0.70 ± 2.53 and 0.82 ± 2.62, respectively ($P < 0.001$). At week 54, mean ± SD changes from baseline in the total Sharp/van der Heijde score were −0.94 ± 3.40 in patients randomized to receive infliximab and 0.53 ± 2.60 in those receiving placebo/infliximab ($P = 0.001$).**

Conclusion. **Infliximab significantly inhibits radiographic progression in patients with PsA as early as 6 months after starting treatment, and the beneficial effect continues through 1 year of infliximab therapy.**

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Psoriatic arthritis (PsA) is a destructive and erosive arthritis that occurs in patients with psoriasis at a reported prevalence of 6–39% (1–4). Most importantly, this disease is associated with chronic inflammation and progressive radiographic damage in a substantial proportion of patients (5–9). Recent evidence confirmed previous reports that the number of actively inflamed joints has predictive value in determining the progression of radiographic damage (10). The inflammatory response in PsA is mediated by the inflammatory cytokine tumor necrosis factor α (TNFα) (11–17). Indeed, anti-TNFα agents, including monoclonal antibodies such as infliximab and adalimumab as well as the soluble TNF-receptor fusion protein etanercept, have been shown to produce significant clinical responses in patients affected by PsA (18–25).

Results from the double-blind, placebo-controlled portion (through week 24) of the Induction and Maintenance Psoriatic Arthritis Clinical Trial 2 (IMPACT 2) showed that infliximab reduced the signs and symptoms of active PsA, including associated psoriasis, dactylitis, and enthesopathy, and improved physical function and quality of life in these patients (21,26). The safety and clinical efficacy results through 1 year have been published separately (22). This report presents data from IMPACT 2 pertaining to the structural damage in patients with PsA treated with infliximab through 1 year.

In IMPACT 2, structural damage was measured using the Sharp/van der Heijde modified scoring method for PsA (27). This modification evaluates erosion and joint space narrowing (JSN) in both the hands and the feet, including the distal interphalangeal (DIP) joints of the hands, which are commonly involved in PsA. In addition, radiographic features characteristic of PsA, including pencil-in-cup and gross osteolysis deformities, were assessed separately. The results of the radiography analyses presented herein provide insight into the onset and extent of benefit from infliximab treatment evident on joint radiographs from patients with PsA, the magnitude of changes in radiography scores, and the baseline disease characteristics that may be predictive of greater radiographic progression and that might therefore benefit from treatment.

PATIENTS AND METHODS

Patients. The study group comprised patients with an established diagnosis of PsA of ≥6 months' duration, in whom the response to treatment with disease-modifying antirheumatic drugs (DMARDs) or nonsteroidal antiinflammatory drugs (NSAIDs) had been inadequate. At the time of enrollment, patients were required to have active PsA, defined as the presence of ≥5 swollen and ≥5 tender joints (based on joint counts of 66 and 68, respectively), a C-reactive protein (CRP) level ≥15 mg/liter and/or morning stiffness lasting 45 minutes or longer, an active psoriatic plaque ≥2 cm in diameter, and negative results of serum tests for rheumatoid factor. Patients were allowed to have been receiving concomitant therapy with methotrexate (MTX; dosage up to 25 mg/week, with a stable dosage for at least 4 weeks before the first infusion), and they could continue receiving MTX but were not permitted to receive DMARDs other than MTX within 4 weeks of the first infusion. Previous and concomitant treatments with NSAIDs and/or oral corticosteroids (i.e., a stable dosage of ≤10 mg prednisone equivalent/day) for at least 2 weeks before the first infusion were also permitted.

Study design. IMPACT 2 was a phase III, multicenter, double-blind, placebo-controlled study in which eligible patients were randomized (1:1 ratio) to receive infusions of either infliximab (Remicade; Centocor, Inc., Malvern, PA) or placebo. Patients initially assigned to placebo received placebo at weeks 0, 2, 6, 14, and 22, and then crossed over to receive infliximab (5 mg/kg) at weeks 24, 26, 30, 38, and 46. Patients initially assigned to infliximab received infliximab (5 mg/kg) at weeks 0, 2, 6, 14, 22, 30, 38, and 46; in order to maintain blinding, these patients also received placebo infusions at weeks 24 and 26.

Any patient in either treatment group with <10% improvement from baseline in both the swollen joint count and the tender joint count entered an early escape phase at week 16, with patients randomized to the placebo group receiving infliximab (5 mg/kg) at weeks 16, 18, 22, 30, 38, and 46. In order to maintain blinding, patients randomized to the infliximab group who entered an early escape phase received placebo at weeks 16 and 18 but continued to receive the same dose of infliximab through week 46. In any patient randomized to the infliximab group who achieved <20% improvement from baseline in the total number of swollen and tender joints combined, the dose of infliximab was escalated to 10 mg/kg at weeks 38 and 46.

Study procedures and evaluations. Single posteroanterior radiographs of the hands and anteroposterior radiographs of the feet were obtained at baseline and weeks 24 and 54 or at study termination. Original films were sent to Bio-Imaging Technologies, (Newtown, PA) for digitization. Two trained independent readers, who were blinded to patient identity, treatment arm, and radiograph sequence, independently assessed the digitized images. Average scores from the 2 readers were used for the analyses. If there was a predefined discrepancy in the change from baseline to week 24 in the total Sharp/van der Heijde score (i.e., >10) between the 2 readers, a third independent reader (i.e., an adjudicator who was blinded to patient identity, treatment assignment, film sequence, and scores from the other readers) also scored the radiographs; the reader's score that was closer to the adjudicator's score was used for the analysis.

Erosion, JSN, and total radiography scores (i.e., the sum of erosion and JSN scores) were determined using a modification of the Sharp/van der Heijde scoring method that included, in addition to the joints scored in rheumatoid arthritis (RA) (28), the second through fifth DIP joints of each hand, to address the joint involvement considered character-

Table 1. Baseline characteristics of the patients*

Characteristic	Placebo (n = 100)	Infliximab, 5 mg/kg (n = 100)
Female sex, %	49.0	29.0
Age, years	46.5 ± 11.3	47.1 ± 12.8
Psoriatic arthritis subtype, %		
Arthritis involving distal interphalangeal joints	23.0	26.0
Arthritis mutilans	2.0	1.0
Asymmetric peripheral arthritis	22.0	18.0
Polyarticular arthritis	47.0	53.0
Spondylitis with peripheral arthritis	6.0	2.0
Disease duration, years		
Psoriatic arthritis	7.5 ± 7.8	8.4 ± 7.2
Psoriasis	16.8 ± 12.0	16.2 ± 11.0
At least 3% body surface area affected with psoriasis, %	87	83
Psoriasis Area and Severity Index score (range 0–72)	10.2 ± 9.0	11.4 ± 12.7
Modified Sharp/van der Heijde score†		
Total	39.1 ± 82.8	30.3 ± 61.4
Median (range)	4.5 (0.0–457.0)	6.0 (0.0–443.3)
Erosion	20.8 ± 46.7	16.1 ± 35.0
Median (range)	2.5 (0.0–267.0)	2.5 (0.0–253.8)
Joint space narrowing	18.3 ± 36.9	14.2 ± 27.1
Median (range)	3.0 (0.0–190.0)	2.0 (0.0–189.5)
Hands	23.1 ± 55.9	18.5 ± 40.2
Median (range)	2.5 (0.0–289.0)	2.0 (0.0–286.8)
Feet	16.0 ± 34.9	12.7 ± 28.0
Median (range)	1.0 (0.0–168.0)	1.0 (0.0–156.5)
Health Assessment Questionnaire score (range 0–3)	1.2 ± 0.6	1.1 ± 0.6
C-reactive protein, mg/dl	2.3 ± 3.4	1.9 ± 2.1
Medication received at baseline, %		
Methotrexate	45.0	47.0
Oral corticosteroids	10.0	15.0
Nonsteroidal antiinflammatory drugs	73.0	71.0

* Except where indicated otherwise, values are the mean ± SD.
† Median (range) provided due to skewed nature of radiography data. Ninety-seven patients in each group were evaluated for the modified Sharp/van der Heijde score.

istic of PsA. The total radiography score (hands and feet combined) ranged from 0 to 528 (0–360 for the hands and 0–168 for the feet), with higher scores indicating more articular damage. To account for features specific to PsA, pencil-in-cup and gross osteolysis deformities were also scored separately but were not included in the total score. "Radiographic progression" from baseline to week 24 was defined as a change from baseline in the modified Sharp/van der Heijde score over this time period that was greater than the smallest detectable change (SDC) (29). In addition, we determined the proportion of patients with a change in the total Sharp/van der Heijde score >0.5.

Statistical analysis. The 2 coprimary efficacy end points of this study were the proportion of patients who achieved American College of Rheumatology 20% criteria for improvement (ACR20) in RA (30) at week 14, and the change from baseline in the total modified Sharp/van der Heijde score at week 24. The analysis of the structural damage end point was to be performed as a coprimary end point contingent on the success of the statistical test on the improvement in the ACR20 end point. A 2-sided alpha level of 0.05 was designated for each of the coprimary end point analyses. With 100 patients in each group, the study had at least 90% power to detect a significant treatment-related difference in the signs and symptoms of arthritis (the proportion of ACR20 responders at week 14), as described previously (21). Initially, the study was not powered to detect a significant difference in the prevention of structural damage.

Using the read from the 2 readers for all patients and the reread data for 10% of randomly selected patients, an interreader intraclass correlation coefficient (ICC), and a read–reread (intrareader) ICC for the total modified Sharp/van der Heijde scores were estimated at baseline and at weeks 24 and 54. In order to assess reader consistency, changes from baseline in the total modified Sharp/van der Heijde score at both week 24 and week 54 were compared between readers.

The primary analysis was based on all randomized patients according to the treatment assigned, regardless of the actual treatment received. For the radiography coprimary end point, patients assigned to receive placebo who entered the early escape phase (47 of 100 patients) were analyzed within the placebo group despite receiving active treatment for 8 weeks. Because this was an intent-to-treat analysis, missing data were imputed by linear extrapolation or by assigning a score of zero for change (see radiography results below for further details). Several sensitivity analyses were performed to assess the impact of missing value imputation (i.e., analysis based on observed data for patients who completed 24 weeks

Table 2. Change from baseline in modified Sharp/van der Heijde score, and proportion of patients with radiographic progression*

	Week 24			Week 54		
	Placebo (n = 100)	Infliximab, 5 mg/kg (n = 100)	*P*	Placebo/infliximab (n = 100)	Randomized infliximab, (n = 100)	*P*
Change from baseline in Sharp/van der Heijde score						
Total, mean ± SD	0.82 ± 2.62	−0.70 ± 2.53		0.53 ± 2.60	−0.94 ± 3.40	
Median	0.0	0.0	<0.001	0.0	0.0	0.001
Range	−4.5, 12.7	−15.0, 4.0		−6.1, 12.1	−29.0, 3.0	
Erosion, mean ± SD	0.51 ± 1.68	−0.56 ± 2.09		0.42 ± 2.02	−0.61 ± 2.16	
Median	0.0	0.0	<0.001	0.0	0.0	<0.001
Range	−3.0, 9.0	−12.0, 3.0		−3.8, 12.1	−18.0, 2.0	
JSN, mean ± SD	0.31 ± 1.29	−0.14 ± 0.81		0.11 ± 0.97	−0.33 ± 1.37	
Median	0.0	0.0	0.013	0.0	0.0	0.047
Range	−2.5, 9.5	−4.0, 2.5		−3.0, 6.0	−11.0, 1.0	
Hands, mean ± SD	0.74 ± 2.30	−0.31 ± 1.40		0.54 ± 2.38	−0.45 ± 1.83	
Median	0.0	0.0	<0.001	0.0	0.0	0.004
Range	−2.0, 12.7	−7.0, 4.0		−5.6, 12.1	−12.5, 3.0	
Feet, mean ± SD	0.08 ± 0.94	−0.39 ± 1.50		−0.01 ± 1.03	−0.48 ± 2.28	
Median	0.0	0.0	0.003	0.0	0.0	0.080
Range	−4.5, 5.6	−10.0, 3.0		−3.5, 9.0	−22.0, 0.50	
Radiographic progression from baseline, % of patients						
Total score	12	3	0.017	8	1	0.018
Erosion score	12	2	0.006	9	1	0.010
JSN score	11	1	0.003	6	0	0.013

* Patients in the placebo/infliximab group were initially randomized to receive placebo and received infliximab, 5 mg/kg, starting at either week 16 or week 24. Patients in the randomized infliximab group were initially randomized to receive infliximab 5 mg/kg, and either received that dose of infliximab throughout the study or had the dose escalated to 10 mg/kg at week 38. Radiographic progression is defined as a change greater than the smallest detectable change (SDC); SDCs for total, erosion, and joint space narrowing (JSN) scores are 2.7, 1.8, and 1.5, respectively.

of treatment, analysis based on observed data regardless of whether patients completed 24 weeks of treatment, and analysis using only linear extrapolation to impute the data). To further test the robustness of the primary analysis, additional sensitivity analyses were conducted, including evaluation of "pure placebo" patients (those who did not enter the early escape phase) versus patients randomized to the infliximab group, and evaluation of the effect of adjudication on treatment effect.

Descriptive summary statistics (n, mean, SD, median, interquartile range, minimum, and maximum) were used to summarize continuous variables, and percentages were calculated for discrete variables. The coprimary end point of change from baseline in the total modified Sharp/van der Heijde score at week 24 and other secondary end points with continuous data were analyzed using a 2-sided F test based on an analysis of variance (ANOVA) method on the van der Waerden normal scores of these end points. Baseline MTX use (Yes/No) was included as a factor in the ANOVA model. Categorical data were analyzed using the Cochran-Mantel-Haenszel chi-square test stratified by baseline MTX use.

To evaluate the consistency of the primary radiography end point, the median difference and 95% confidence interval (95% CI) were determined for subgroups prespecified in the analysis plan, including baseline disease characteristics (e.g., PsA duration), baseline measures of systemic inflammation (e.g., CRP level), prior and concomitant medications for PsA (e.g., baseline MTX use), and baseline radiography scores. The comparative response rates for infliximab and placebo were determined based on the median difference between the treatment groups, with any value >0 assumed to be a greater response rate for infliximab. The Hodges-Lehmann method was used to determine whether subgroup differences in 95% CIs overlapped the 95% CIs for all patients, which would be indicative of a treatment effect within that subgroup. *P* values were calculated from an ANOVA model based on the normal van der Waerden test score. Baseline MTX use was included as a factor for all subgroup analyses, except those based on prior and concomitant medications.

In addition, several exploratory analyses predefined in the analysis plan were performed, including assessment of the number of patients and number of joints with pencil-in-cup and gross osteolysis deformities and changes in the total Sharp/van der Heijde score using the original method, without adding hand DIP joints.

RESULTS

Baseline characteristics and patient disposition. Previous reports have described patient disposition through week 24 and week 54 (21,22). Of the 200 patients enrolled in the study, 166 completed the study through week 54. Forty-seven patients randomized to receive placebo entered the early escape phase at week 16, and 15 patients randomized to receive infliximab 5 mg/kg had the dose escalated to 10 mg/kg starting at

week 38. The demographic and baseline disease characteristics of the 2 treatment groups were similar, except for a lower proportion of women in the infliximab group compared with the placebo group (29% versus 49%) (Table 1). Patients enrolled in the study had comparable levels of structural damage at baseline.

Radiography end points. Eighty-six percent of patients assigned to receive infliximab and 85% of those assigned to receive placebo had paired baseline (week 0) and week 24 radiography data. For week 54 analyses, 78% of patients receiving infliximab and 76% of those receiving placebo had paired baseline and week 54 radiographs. Prespecified rules for missing data imputation were used for calculating scores for patients with missing data, including linear extrapolation or, if there were insufficient time points for extrapolation, using the median of the change in the total scores based on all patients within the same MTX stratification (median changes were 0, both for patients receiving MTX and those not receiving MTX). Because radiography scores are not normally distributed, imputing the missing values with a median of 0 was assumed to have less bias effect on the difference between groups compared with using a mean.

At week 24, patients in the group receiving infliximab (5 mg/kg) had significantly ($P < 0.001$) less structural damage compared with the placebo group, as demonstrated by the mean ± SD changes from baseline in the total Sharp/van der Heijde modified score (–0.70 ± 2.53 and 0.82 ± 2.62 for the infliximab and placebo groups, respectively) (see Table 2 for medians). The results of all sensitivity analyses performed, including consistency of the results irrespective of data imputation, evaluating only patients assigned to receive placebo who did not enter the early escape phase, or evaluating the effect of adjudication, confirmed the robustness of the primary radiography end point analysis, indicating a significant difference between the placebo and infliximab groups.

The inhibition of structural damage at week 24 was sustained through week 54 in patients randomized to receive infliximab, and inhibition was also observed at week 54 in patients who crossed over from placebo to infliximab 5 mg/kg. Placebo-randomized patients who switched to infliximab demonstrated a mean ± SD change of −0.29 ± 1.98 in the total Sharp/van der Heijde score from week 24 to week 54, as compared with a change of 0.82 ± 2.62 during the first 24 weeks of placebo treatment. Scores remained stable in patients randomized to the infliximab group, with a mean ± SD change of –0.24 ± 2.45 from week 24 to week 54.

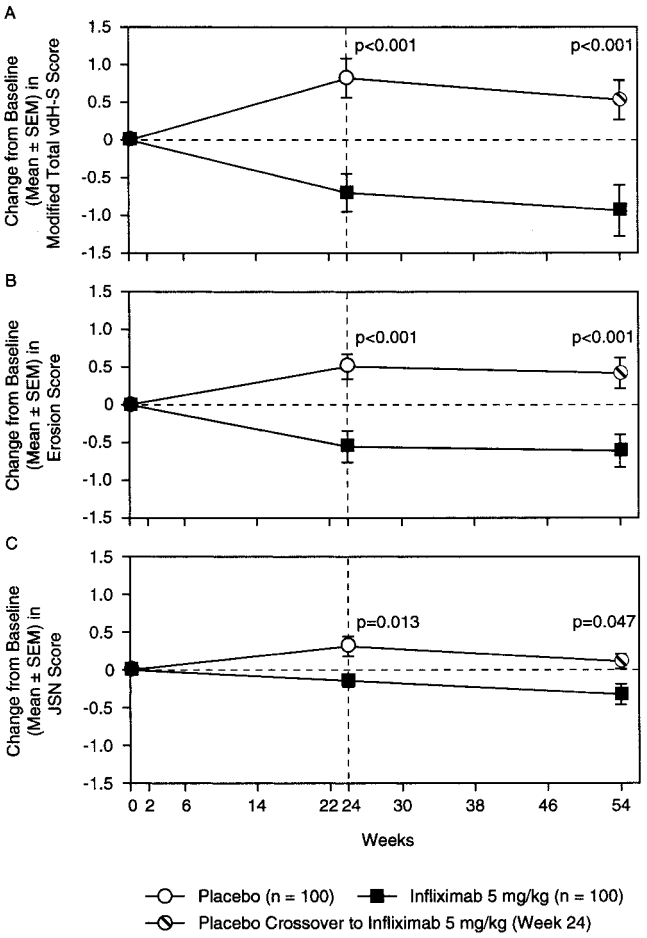

Figure 1. Mean ± SEM changes from baseline to week 54 in **A,** the modified total Sharp/van der Heijde score (vdH-S), **B,** the erosion score, and **C,** the joint space narrowing (JSN) score. At week 24, changes in scores in the infliximab group and the placebo group were significantly different. At week 54, changes in scores in the randomized infliximab group and the placebo/infliximab group were significantly different.

Despite improvement from week 24 to week 54 in placebo-randomized patients who crossed over to infliximab at week 24, the mean change from baseline in the total modified Sharp/van der Heijde score at week 54 remained significantly lower ($P = 0.001$) in the group randomized to receive infliximab compared with the placebo/infliximab group (Table 2 and Figure 1). When hands ($P < 0.001$) and feet ($P = 0.003$) were assessed separately, and erosions ($P < 0.001$) and JSN ($P = 0.013$) were assessed separately at week 24, significant differences were also observed in favor of infliximab 5 mg/kg over placebo for all assessments (Table 2 and Figure 1). Significant differences in scores between the

groups were maintained for the total score, and hand, erosion, and JSN scores through week 54.

At week 24, a significantly lower proportion of patients in the group receiving infliximab 5 mg/kg had a change in the total Sharp/van der Heijde score greater than the SDC (2.7) when compared with the placebo group (3% versus 12%; $P = 0.017$); the significant difference between the group randomized to receive infliximab and the placebo/infliximab group was maintained through week 54 (1% versus 8%; $P = 0.018$) (Table 2). The same was true for erosion and JSN scores, which were analyzed separately, at both time points (Table 2). Also of note, 22% and 18% of the patients in the placebo group showed changes in the total radiography score >0.5 through week 24 and week 54, respectively, as compared with only 10% and 8%, respectively, of patients in the infliximab group.

The bootstrap 95% CI of the mean change in the modified Sharp/van der Heijde score for the infliximab group included only negative values (−1.24, −0.25), while that for the placebo group included only positive values (0.35, 1.35). In addition, more patients had a negative change in the modified Sharp/van der Heijde score compared with a positive change in score (33 and 13, respectively; $P = 0.003$ by sign test) in the infliximab group, and the observed mean magnitude of change was larger in patients with negative change values than in those with positive change values (2.70 and 1.49, respectively).

The cumulative probability plots of changes in the total modified Sharp/van der Heijde score through week 24 and week 54 (Figure 2) showed that the curves for patients treated with infliximab lie to the right of the curves for placebo-treated patients, indicating that fewer infliximab-treated patients had radiographic progression, and that there was a smaller amount of radiographic progression per patient among the infliximab-treated patients. Through week 54, 59% and 56% of patients in the infliximab and placebo/infliximab groups, respectively, had a change of 0 from baseline. However, 22% of patients in the placebo group showed positive changes in the scores as compared with only 9% of patients in the infliximab group, while 32% of patients in the infliximab group showed negative changes in the scores as compared with 22% of those in the placebo group.

At both week 24 and week 54, no between-group differences were observed for the number of joints and the number of patients with the PsA-specific radiographic features of pencil-in-cup and gross osteolysis deformities. The number of patients with these deformities at baseline was low (7.2% according to reader 1 and 10.1% according to reader 2), and these percentages did not change for either reader during the study. Among >8,000 scored joints, 31 were considered to have pencil-in-cup or gross osteolysis deformities by reader 1, and reader 2 assessed 73 joints as having these deformities. Across both readers and within each treatment group, no changes from baseline were noted in the number of joints with pencil-in-cup or gross osteolysis deformities at week 24 and week 54.

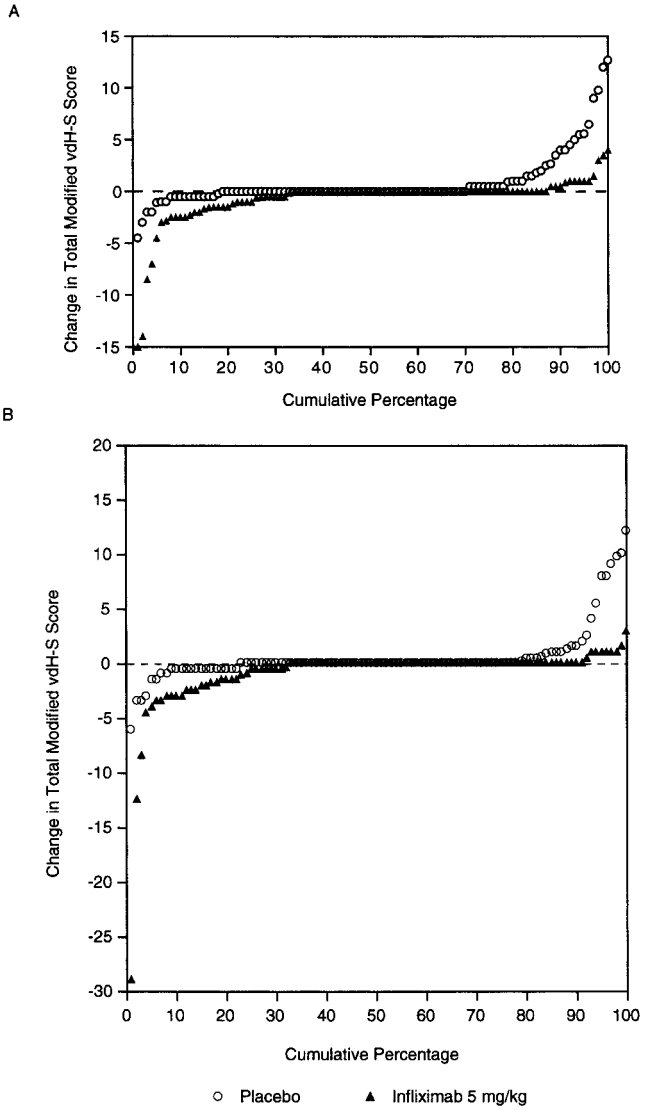

Figure 2. Probability plot of change in the total modified Sharp/van der Heijde (vdH-S) scores in the group of patients receiving infliximab at a dose of 5 mg/kg and the group receiving placebo, through week 24 (**A**) and week 54 (**B**).

Changes from baseline in the total Sharp/van der

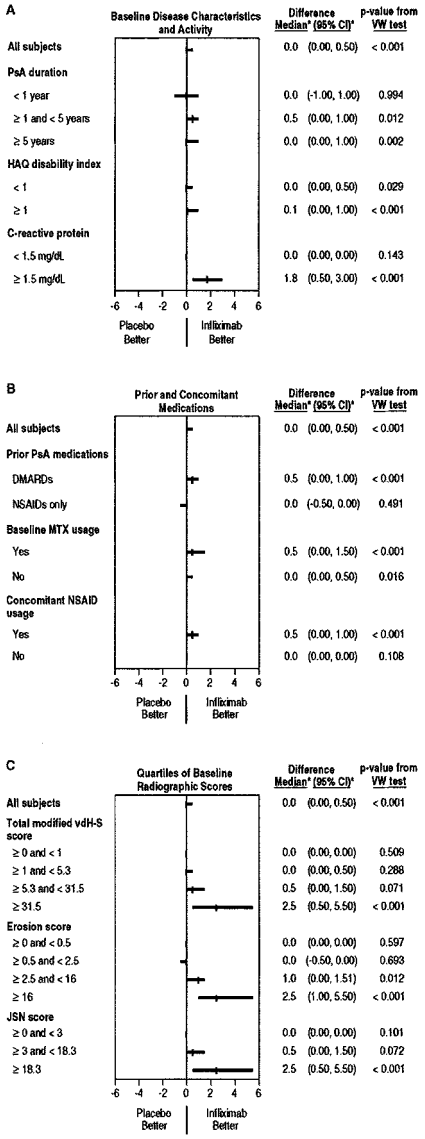

Figure 3. Median of the differences between treatment groups in the change from baseline in the total modified Sharp/van der Heijde (vdH-S) score at week 24 (vertical bars) and associated 95% confidence intervals (95% CIs) (horizontal bars) for all randomized patients. **A,** Subgroups defined by baseline disease characteristics and activity. **B,** Subgroups defined by prior and concomitant medications. **C,** Subgroups defined by quartiles of baseline radiography scores. VW test = van der Waerden test; PsA = psoriatic arthritis; HAQ = Health Assessment Questionnaire; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs; MTX = methotrexate; JSN = joint space narrowing. * = median of the differences and the corresponding 95% CIs were estimated using the Hodges-Lehmann method.

Heijde, erosion, and JSN scores assessed at weeks 24 and 54 using the original scoring method (i.e., without the addition of the hand DIP joints) were consistent with those obtained using the Sharp/van der Heijde modified scoring method for PsA and demonstrated significant difference between the treatment groups. However, as expected, scores obtained using the original scoring method were numerically lower than those obtained using the modified method for PsA (data not shown).

Consistency across readers. The ICC, the inter-reader reliability coefficient, and the read–reread coefficient estimated at baseline, week 24, and week 54 for the variability of the Sharp/van der Heijde modified scoring method for PsA ranged from 0.97 to 1. With regard to the change from baseline in the total modified Sharp/van der Heijde score by reader, the 2 readers were consistent in their agreement on treatment effect, with both readers producing mean scores that demonstrated that the placebo group showed significantly more progression of structural damage at week 24. Similar to week 24, a consistent treatment effect was observed, regardless of the reader, at week 54.

Subgroup analyses. The consistency of the treatment effects on the primary structural damage end point (i.e., change from baseline in the total modified Sharp/van der Heijde score at week 24) was evaluated across subgroups defined by baseline disease characteristics and disease activity (including baseline CRP level), prior and concomitant medications for PsA and psoriasis (including baseline MTX use), and baseline radiography scores. In addition, an ANOVA model on the van der Waerden normal scores of change at week 24 was fitted with treatment effect, MTX use, PsA duration, CRP level, Health Assessment Questionnaire (HAQ) score (31), modified Sharp/van der Heijde score quartiles, and interactions of treatment effect with all other factors. The model suggested that there was a significant treatment effect and a significant MTX effect, and also that there were significant treatment interactions with baseline total modified Sharp/van der Heijde scores and baseline CRP concentrations.

Figure 3 shows that the median of the differences between the treatment groups in the change from baseline in the total modified Sharp/van der Heijde score generally exceeded zero and displayed overlapping 95% CIs across most subgroups, indicating a consistent treatment effect in favor of infliximab compared with placebo. In general, the median of the differences between the treatment groups was greater in the subgroups consisting of patients with features of more severe disease at baseline, including prior use of DMARDs, baseline MTX use, baseline corticosteroid use, longer PsA duration (≥1 year), higher CRP level (≥1.5 mg/dl), higher HAQ scores (≥1), and higher total modified

Sharp/van der Heijde score (≥31.5), erosion score (≥16), and JSN score (≥18.3).

DISCUSSION

These 1-year results from IMPACT 2 document the early, continuous, and significant inhibition of structural damage progression in patients with PsA treated with infliximab. The beneficial effect of infliximab treatment was seen as early as 6 months after the start of treatment, which may have implications both for identifying the optimal timing of initiating treatment for inhibiting structural damage in PsA and for addressing the ethical concerns of maintaining the placebo arm for extended periods of time. Although only a minority of patients demonstrated changes in radiography scores, factors that may be associated with radiographic progression were identified. The scoring methods used to assess radiographic damage in RA and to evaluate erosions and JSN can be used to assess progression of structural damage in patients with PsA. However, the usefulness of scoring the features characteristic of PsA seems very limited and will require further evaluation.

In the placebo-controlled portion of the study (i.e., through week 24), patients treated with infliximab demonstrated significantly less progression of structural damage compared with patients receiving placebo, across multiple radiography analyses, including changes in total Sharp/van der Heijde, erosion, JSN, hand and foot scores, radiographic progression assessment based on a change in total score greater than the SDC and >0.5, and multiple sensitivity analyses addressing the effect of data imputation, adjudication, and early escape. Specifically, there was a significant difference in favor of infliximab treatment despite the fact that the placebo group included patients who entered the early escape phase and received 3 infusions of infliximab prior to week 24, which could actually imply that the extent of radiographic progression in the placebo group was underestimated.

Interestingly, it can be observed from the probability plots that many infliximab-treated patients indeed showed negative progression scores, and that more patients had a negative change in the modified Sharp/van der Heijde score than a positive change, indicating that repair of structural damage might occur. These findings are corroborated by the fact that the bootstrap 95% CI of the mean change in the modified Sharp/van der Heijde score for the infliximab group included only negative values, while that for the placebo group included only positive values (32), as well as by the observation that the mean magnitude of change was larger in patients with negative change values than in those with positive change values.

Through week 54, patients randomized to receive infliximab continued to show no radiographic progression. Starting at week 24 (i.e., after crossing over to active treatment) and continuing through week 54, patients in the placebo group showed less progression of structural damage compared with the progression that occurred during the placebo-controlled portion of the study. These results indicate that delayed treatment with infliximab still benefits the patients, but to a lesser degree when compared with the benefit of starting treatment earlier.

The results of this study show that infliximab significantly inhibited the progression of structural damage as early as 6 months after beginning treatment. This cutoff point is significant from both a clinical perspective and an ethical standpoint. Before anti-TNF treatment was available for use in PsA, it was acceptable within the medical community to obtain radiographs of joint damage every 2 years in patients with PsA (33). However, now that the substantial clinical efficacy of TNF inhibitors is well established (18–25), it may not be necessary to wait 2 years before starting more aggressive treatment. Similarly, continuing to offer placebo for long periods of time to patients with active disease in clinical trials may be ethically problematic (34). The results of this study show that the 6-month period before crossing over to active treatment with the possibility of early escape is not only sufficient to demonstrate that infliximab significantly inhibits the progression of structural damage but also satisfies the ethical need to provide placebo-randomized patients with active treatment as early as possible.

In this study, a consistently beneficial effect on the inhibition of structural damage was observed across baseline disease characteristics and activity, prior and concomitant medications, and baseline radiography scores. Importantly, the between-group difference in response to treatment was greater in subgroups defined by patients with more severe disease, including those with prior use of DMARDs, baseline corticosteroid use, baseline MTX use, baseline CRP level ≥1.5 mg/dl, baseline HAQ score of ≥1, or baseline total modified Sharp/van der Heijde score of ≥31.5. This appears to indicate that, although infliximab may potentially slow radiographic progression in patients with less severe disease, the benefit from infliximab in terms of inhibiting radiographic damage may be maximal in patients with more severe disease at baseline. Indeed, progression of

damage is more likely to occur in patients with more severe disease at baseline (10).

Scoring methods developed to evaluate the extent of radiographic damage in RA have been extrapolated for use in assessing PsA. As described previously, the van der Heijde modification of the Sharp score, commonly used to assess structural changes in patients with RA, evaluates joint erosion and JSN in selected joints (35–37). The analysis of radiography data in the current study employed a further modification of the Sharp/van der Heijde score that assessed both the hands, with the inclusion of hand DIP joints, and the feet. In addition, the pencil-in-cup deformity and gross osteolysis, which reflected typical features of joint involvement in PsA, were assessed. The goal of this novel approach was to provide a more comprehensive evaluation that was especially appropriate for patients with PsA. Indeed, the Sharp/van der Heijde modified scoring method for PsA performed well in this analysis of radiographic changes in patients with PsA and enabled differentiation between treatment groups with good consistency between the readers, although the addition of hand DIP joints and gross osteolysis/pencil-in-cup assessments did not add significantly to the original van der Heijde score in this patient population.

Interestingly, in this study of PsA, the number of joints or patients with the characteristic features of pencil-in-cup or gross osteolysis deformities was low and did not change from baseline through week 54 in either treatment group. This indicates that these features are not useful for evaluating treatment effect in patients with PsA over followup periods of 54 weeks. These findings are consistent with those from the earlier IMPACT study of 104 patients with active PsA, in which radiography scores were determined using the same Sharp/van der Heijde modified scoring method for PsA (19). Similarly, in a placebo-controlled study of etanercept at a dosage of 25 mg twice weekly in patients with PsA, the proportion of patients with several features specific to PsA (e.g., pencil-in cup deformity, digital tuft resorption, ankylosis, joint space widening, and juxtaarticular and shaft periostitis) reportedly did not change from baseline to week 24 in either treatment group, further substantiating the concept that these features are not useful for assessing treatment effect in PsA over a followup period of up to 54 weeks (24).

In summary, results from IMPACT 2 provide evidence for the early and sustained inhibition of structural damage in patients with PsA treated with infliximab. Infliximab significantly inhibited the progression of radiographic damage as early as 6 months following the start of treatment, and this effect was maintained through 1 year.

AUTHOR CONTRIBUTIONS

Dr. van der Heijde had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Van der Heijde, Kavanaugh, Gladman, Antoni, Krueger, Guzzo, Dooley, Beutler.

Acquisition of data. Van der Heijde, Kavanaugh, Gladman, Antoni, de Vlam, Geusens, Birbara, Halter.

Analysis and interpretation of data. Van der Heijde, Kavanaugh, Gladman, Antoni, Krueger, Guzzo, Dooley, de Vlam, Geusens, Beutler.

Manuscript preparation. Van der Heijde, Kavanaugh, Gladman, Antoni, Guzzo, de Vlam, Geusens, Birbara, Beutler, and Cynthia Arnold and Michelle Perate (nonauthors; Centocor, Inc.).

Statistical analysis. Zhou, Dooley.

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