Open Label Study to Assess Infliximab Safety and Timing of Onset of Clinical Benefit Among Patients with Rheumatoid Arthritis

WILLIAM J. SHERGY, REUBEN A. ISERN, DAVID A. COOLEY, JOHN L. HARSHBARGER, J. EUGENE HUFFSTUTTER, GORDON M. HUGHES, ELIZABETH A. SPENCER-SMITH, ALLAN L. GOLDMAN, SANFORD H. ROTH, J. SCOTT TODER, DIANA WARNER, ADRIENNE QUINN, GREGORY F. KEENAN, THOMAS F. SCHAIBLE, and THE PROMPT STUDY GROUP

ABSTRACT. ***Objective.*** To assess the timing of onset of clinical benefit following the initial infusion of infliximab and to obtain additional safety experience of infliximab when given in an office setting to patients with rheumatoid arthritis (RA). In addition, the safety of reducing the infusion time from 2 hours to 1 hour was evaluated.

Methods. Patients (n = 553) with active RA despite receiving methotrexate (MTX) were treated with infliximab 3 mg/kg given over 2 h at baseline (Week 0), and Weeks 2, 6, and 14 in this multicenter open-label trial. Patients continued to receive a stable dose of MTX (≥ 7.5 mg/wk). At selected sites, patients tolerating the first 4 infusions were eligible to receive 2 additional infusions at twice the usual infusion rate (given over 1 h). Patients returned for efficacy assessments at 48 h following the initial infusion and several times throughout study participation.

Results. By 48 h following the first infusion, significant ($p < 0.001$) improvements were observed in duration of morning stiffness (34% mean improvement), physician's global disease assessment scores (30%), patient's global disease assessment scores (25%), and patient's pain assessment scores (30%). By Week 16, 52 to 63% mean improvements in these efficacy variables were observed ($p < 0.001$); the significant improvement was maintained through the end of study participation in the subset of patients who received the additional 1 h infliximab infusions. Through 16 weeks, 10% (54/553) of patients reported an adverse event associated with at least 1 of the 4 infusion procedures; the majority were mild and transient in nature. In the subset of 197 patients who received 2 additional infusions over 1 h, no increase in the frequency or severity of infusion-related adverse events was observed compared to the 2 h infusion.

Conclusion. Infliximab administered to patients with RA in an outpatient setting resulted in significant clinical improvement within 48 h that was sustained with additional infusions. Approximately 10% of patients experienced an infusion reaction, highlighting the need for direct supervision over patient treatment. Patients who tolerated infliximab infusions given over 2 h also tolerated a 1 h infusion. (J Rheumatol 2002;29:667–77)

Key Indexing Terms:
INFLIXIMAB RHEUMATOID ARTHRITIS TUMOR NECROSIS FACTOR-α
DMARD METHOTREXATE

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W.J. Shergy, MD, Rheumatology Associates of North Alabama PC, Fellow Member, Huntsville, Alabama; R.A. Isern, MD, Fellow Member, Arthritis and Rheumatology Associates of SE Texas, Beaumont, TX; A. Cooley, MD, Fellow Member, Mid-American Rheumatology Consultant, Overland Park, Kansas; J.L. Harshbarger, MD, Fellow Member, Carolina Arthritis Associates, Wilmington, North Carolina; J.E. Huffstutter, MD, Fellow Member, Chattanooga, Tennessee; G.M. Hughes, MD, Fellow Member, Rheumatology Section, Medical Consultants Inc, Muncie, Indiana; E.A. Spencer-Smith, MD, Fellow Member, Santa Rosa, California; A.L. Goldman, MD, Fellow Member, Milwaukee, Wisconsin; S.H. Roth, MD, Fellow Member, ArthroCare, Arthritis Care & Research, Phoenix, Arizona; J.S. Toder, MD, Fellow Member, Johnston, Rhode Island; D. Warner, RN; G.F. Keenan, MD; T.F. Schaible, PhD, Centocor, Inc, Malvern, Pennsylvania, USA.

Address reprint requests to Dr. W.J. Shergy, Rheumatology Associates of North Alabama PC, 210 Sivley Rd., Suite 600, Huntsville AL, 35801, USA.

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Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine that mediates the production of other inflammatory cytokines and plays a key role in the pathophysiology of a number of inflammatory disorders. The chimeric anti-TNF-α monoclonal antibody infliximab (Remicade®) is a potent antiinflammatory agent that binds to TNF-α with high affinity, avidity and specificity, thereby neutralizing its biological activity. Infliximab has received marketing authorization for both Crohn's disease and rheumatoid arthritis (RA) in the United States and the European community.

In a large clinical trial of infliximab in 428 patients with active RA despite methotrexate (MTX) therapy (the ATTRACT trial), it was demonstrated that infliximab is safe and effective in improving the signs and symptoms,

arresting structural damage, and improving functional status/quality of life in patients with refractory RA. In ATTRACT, clinical benefit was demonstrated as early as 2 weeks (the first evaluation time point for efficacy variables) in approximately half of the ultimate responders and was maintained through at least 2 years in approximately 60% of patients[1-3].

While RA is a chronic disease, patients suffer with the challenge of living each day. Consequently, a therapy that provides a rapid benefit to affected individuals would be an attractive feature. The intravenous route of administration and highly stable complexes that infliximab forms with TNF-α[4] allow for rapid and durable neutralization of TNF-α. Since this proinflammatory cytokine appears to be so integral to the inflammatory cascade[5], as evidenced by its triggering of interleukin (IL)-1 downstream in the cascade, a rapid neutralization may provide more immediate relief to patients with RA. In addition, given that infliximab has been provided safely to patients in a number of settings and that it is often administered in the rheumatologist's office, it was considered appropriate to conduct a study assessing the onset of infliximab's clinical benefit in this setting.

Our study (Profiling Remicade Onset with MTX in a Prospective Trial, or PROMPT trial) was conducted to determine the clinical benefit of infliximab 2 days following the initial infusion, as well as to further establish the safety experience of administering infliximab in an in-office setting when given in up to 6 infusions. We also evaluated the tolerability of reducing the infusion time for infliximab administration from 2 h to 1 h.

MATERIALS AND METHODS

Eligibility. Men and women (18 years of age) who had a diagnosis of RA according to the American College of Rheumatology (ACR) criteria were eligible for this multicenter, open-label study of infliximab. Evidence of active disease despite treatment with methotrexate (MTX) (active disease was defined as 6 swollen joints and/or 6 tender joints and morning stiffness $\geq$ 45 min) was required. Eligible patients had to be receiving a stable dose of $\geq$ 7.5 mg/wk of MTX given orally or parenterally and then continue at this dose during the study period. Concurrent treatment with stable regimens of corticosteroids ($\leq$ 10 mg/day), nonsteroidal antiinflammatory drugs (NSAID), and/or disease modifying antirheumatic drugs (DMARD) was permitted. Women of childbearing potential were required to use adequate birth control measures and continue such precautions for 6 mo after receiving the last infliximab infusion. Patients provided written informed consent prior to any protocol-specific procedure. The study was conducted in accordance with regulations governing clinical trials including the US Code of Federal Regulations and the Declaration of Helsinki. Patients provided written informed consent before any study-related procedures were conducted.

Study medication. Five hundred and fifty-three patients were treated with open-label infliximab (Remicade®, Centocor, Inc, Malvern, PA, USA) 3 mg/kg at baseline (Week 0) and Weeks 2, 6, and 14. The study medication was prepared based on the patient's weight. Infliximab was administered via a separate line using the administration supplies provided. The infusion was delivered over 2 h for each of the 4 infusions. For the first and subsequent 2-h treatments when there was no previous infusion-related adverse event, 250 ml was infused over 2 h at an approximate rate of 2 ml/min. Patients with a history of infusion-related reactions had the infusion rate gradually increased from 10 to 250 ml/h over the 2-h infusion period.

Study extension. The original study protocol was amended to allow sites that met prespecified enrollment goals to enroll patients into the study extension: those patients received 2 open-label 1-h infusions of infliximab 3 mg/kg given 8 wks apart. Forty-six sites and 215 patients qualified for participation in the trial extension. Patients were eligible for inclusion in the protocol extension if they had previously tolerated the four 2-h infusions (at Weeks 0, 2, 6, and 14) without any moderate to severe infusion-related reactions or hypersensitivity reactions and had no significant history of cardiac or renal impairment. Patients also were required to provide additional written consent. Patients could have received commercial infliximab prior to receipt of the 1-h infusions to ensure that no more than 8 wks separated consecutive infliximab infusions. Of the 215 eligible patients, 198 chose to participate in the study extension. The recommended infusion schedule for these patients was 100 ml/h for 15 min, followed by 300 ml/h for 45 min if no reaction occurred.

Study procedures and outcomes. Patients received four 2-h infusions at Weeks 0, 2, 6, and 14 (Infusions 1, 2, 3, and 4, respectively), followed by two 1-h infusions 8 wks apart (Infusions 5 and 6). Followup efficacy assessments, including patient assessment of pain, patient global assessment of arthritis, physician global assessment of arthritis, and duration of morning stiffness, were conducted at 48 h and 1, 2, 6, 14, and 16 wks following Infusion 1; prior to Infusions 5 and 6; and 2 wks following Infusion 6. In addition, as a result of a protocol amendment, tender and swollen joint counts were documented at screening, and at 2 wks following Infusions 4 and 6 in subsets of 462 and 191 patients, respectively. Ten centimeter visual analog scales (VAS) were utilized for the patient assessment of pain (ranging from no pain to worst pain), patient global assessment of arthritis (ranging from very well to very poor), and physician global assessment of arthritis (ranging from no arthritis activity to extremely active arthritis). Duration of morning stiffness was measured in minutes. Sixty-six joints were evaluated for swelling (excluding hips), and 68 joints were evaluated for tenderness. Safety evaluations included measurements of vital signs during and immediately after the infusions of infliximab and assessment for adverse events since the previous infusion and during infusions at each of the evaluation visits. Infusion-related adverse events were defined as those occurring either during the infusion or during the 1 h period following completion of the infusion. Adverse events were judged to be mild (caused no limitation of usual activities), moderate (caused some limitation of usual activities), or severe (caused inability to carry out usual activities) by the investigator.

Data evaluation. Percent improvements from baseline for each efficacy variable were summarized at each assessment time. In addition, these data were analyzed using a repeated measures analysis of covariance model with factors for center and assessment time and baseline as a covariate. A random effect for patient within center was also included in the model to account for the intra-patient correlation. At each assessment time point, the hypothesis that the adjusted mean percentage change was 0 was tested using the same model. Reported p values were adjusted for repeated testing using Bonferroni procedure. Adverse event data are presented overall, for the 2 h infusions, and for the 1 h infliximab infusions.

RESULTS

Baseline patient characteristics. Five hundred and fifty-three patients were enrolled at 79 study centers (73 community based, 6 academic centers). A summary of baseline patient characteristics is provided in Table 1. The majority of treated patients were Caucasian women; the mean age of study participants was 58 years. Most patients (92%) were classified as Functional Class II or III. The subset of patients who continued into the extension portion of the trial

Table 1. Baseline demographic and disease characteristics of patients with RA.

Variable	553 Treated Patients
Age, yrs, mean (SD)	57.9 (12.68)
Ethnic origin, No. (%)	
Caucasian	481 (87.0)
Black	42 (7.6)
Hispanic	19 (3.4)
Asian	6 (1.1)
Other	5 (0.9)
Gender, No. (%)	
Male	122 (22.1)
Female	431 (77.9)
Time since diagnosis of RA, yrs	
mean (SD)	12.0 (10.03)
Functional class, No. (%)	
I	42 (7.6)
II	262 (47.4)
III	249 (45.0)

displayed similar baseline characteristics.

Prior and concomitant medications. A summary of common prior DMARD therapy and concomitant medications is provided in Table 2. The majority (83%) of patients had a history of prior use of DMARD in addition to MTX. The agents most commonly used prior to study participation included hydroxychloroquine, gold preparation, sulfasalazine, and leflunomide. The mean (SD) duration of prior MTX therapy was 5.2 ± 4.34 yrs; the mean MTX dose during 4 to 6 wks prior to study entry was 16.0 ± 8.55 mg/wk. Among the 325 patients receiving prednisone at baseline, most patients were receiving doses of 5 mg/day (44% of patients), 7.5 mg/day (8% of patients), or 10 mg/day (22% of patients); baseline prednisone doses ranged from 1.25 to 30 mg/day.

Table 2. Summary of infliximab infusion and prior and concomitant RA medications.

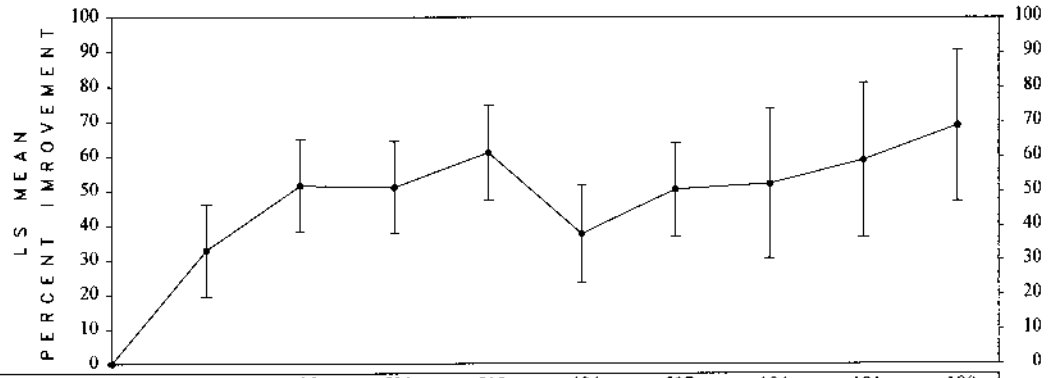
	553 Treated Patients
Infusion location, No. (%)	
Physician's office	72 (91.1)
Infusion center	5 (6.3)
Hospital	2 (2.5)
Common* prior DMARD Use, No. (%)	
None	94 (17.0)
Hydroxychloroquine	299 (54.1)
Gold preparation	249 (45.0)
Sulfasalazine	165 (29.8)
Leflunomide	79 (14.3)
Penicillamine	58 (10.5)
Common** concomitant RA	
Medications, No. (%)	
Methotrexate	548 (99.1)
DMARD other than MTX	
Hydroxychloroquine	105 (19.0)
Leflunomide	40 (7.2)
Sulfasalazine	38 (6.9)
NSAID	469 (84.9)
Folic acid	391 (70.7)
Prednisone	333 (60.2)
Other Analgesics	
Acetaminophen	123 (22.2)
Vicodin	60 (10.8)
Acetylsalicylic acid	54 (9.8)
Alendronate	75 (13.6)
Diphenhydramine	68 (12.3)

* Used by 10%; ** used by 5% or more of patients.

All patients received concomitant medications. A summary of concomitant RA medications taken by 5% or more of patients is provided in Table 2. Most commonly, MTX, NSAID, folic acid, and prednisone were taken in conjunction with infliximab. Through Week 16, 36% of patients received MTX doses (12.5 mg/wk); during the study extension, 41% of patients received MTX doses (12.5 mg/wk). Of note, 66% of patients received MTX as the only DMARD, while 34% of patients received MTX in combination with at least one other DMARD. Common concomitant DMARD included hydroxychloroquine (19% of patients), leflunomide (7%), and sulfasalazine (7%).

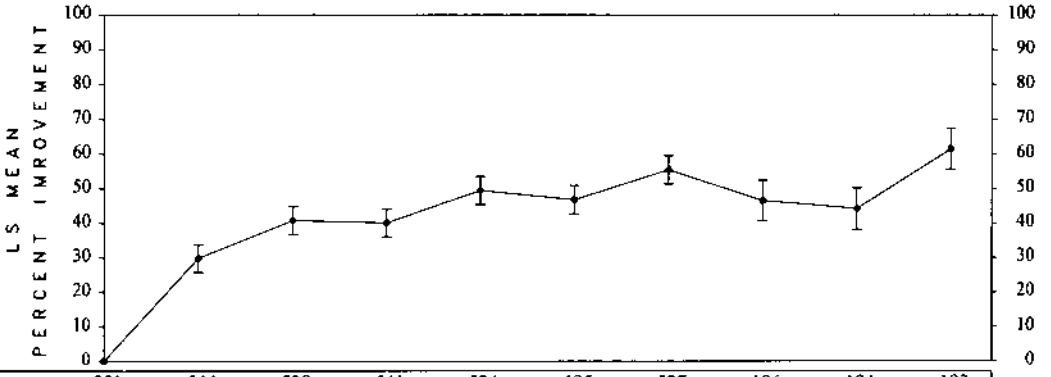
Patient disposition and treatment. All enrolled patients received infliximab. Infliximab infusions were generally administered in the physician's office (91% of sites) or at an infusion center (6% of sites). Less than 3% of participating sites utilized the hospital setting for infliximab administration (Table 2). Eighty-eight percent (484/553) of patients completed all four 2-h infusions of infliximab. Reasons for withdrawal included adverse events (4.5% of patients), treatment failure (2.5%), withdrawal of consent (1.6%), pre-existing violation (1.3%), other reason (1.3%), protocol noncompliance (0.7%), and lost to followup (0.5%). Two hundred and fifteen patients who were treated at a subset of participating sites were eligible to participate in the rapid infusion phase of the trial. One hundred and ninety-eight of these eligible patients chose to receive the 1-h infusion of infliximab; all but one of these patients was treated with infliximab over a 1-h infusion period. Reasons for withdrawal from the study extension included adverse events (4.6% of patients), treatment failure (1.0%), other reasons (1.0%), pre-existing violation (0.5%), and protocol noncompliance (0.5%). One hundred and eighty-two of the original 553 patients (34%), or 92% of the 215 eligible patients, completed the study extension.

Efficacy. Improvement in the signs and symptoms of RA was observed by 48 h following the first infusion, as displayed in Figure 1. At this early time point, morning stiffness, physician's global disease assessment, patient's global disease assessment, and patient's pain assessment scores were improved by 25 to 34% ($p < 0.001$). By Week 16, 52 to 63% mean improvements in these efficacy variables were observed ($p < 0.001$). Results of swollen and tender joint counts performed in a subset of patients showed significant



N in group	553	534	528	531	513	484	517	194	181	190
Mean % Improvement		33.6	52.2	52.1	62.0	38.0	51.5	51.9	60.0	69.8
SE of Mean % Improvement		5.10	1.99	3.74	4.03	12.21	10.72	5.96	4.56	3.96
LS Mean % Improvement (b)		32.9	51.5	51.0	61.0	37.6	50.4	52.1	58.9	68.9
SE of LS Mean % Improvement (b)		6.80	6.84	6.82	6.94	7.12	6.91	11.00	11.36	11.11
Upper 95% Limit (b)		46.2	65.0	64.4	74.6	51.6	64.0	73.6	81.2	90.6
Lower 95% Limit (b)		19.6	38.1	37.7	47.4	23.6	36.9	30.5	36.6	47.1
p-Value (b)		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
INFUSION NUMBER	#1			#2	#3	#4		#5	#6	POST
TIMEPOINT	WEEK 0	DAY 2	WEEK 1	WEEK 2	WEEK 6	WEEK 14	WEEK 16			INF. 6

Figure 1A. Duration in morning stiffness. Least squares (LS) mean percentage improvement (a) from baseline in patients who received at least one infusion. a: Percentage of improvement = 100 × (Baseline Score–Timepoint Score)/Baseline Score. b: Based on repeated measures ANCOVA model on percentage of improvement with factors for center and time and baseline as covariate and a random effect for patient within center. Patients with baseline = 0 were excluded. P values are for testing adjusted mean = 0. P values were adjusted for repeated testing using Bonferroni procedure.

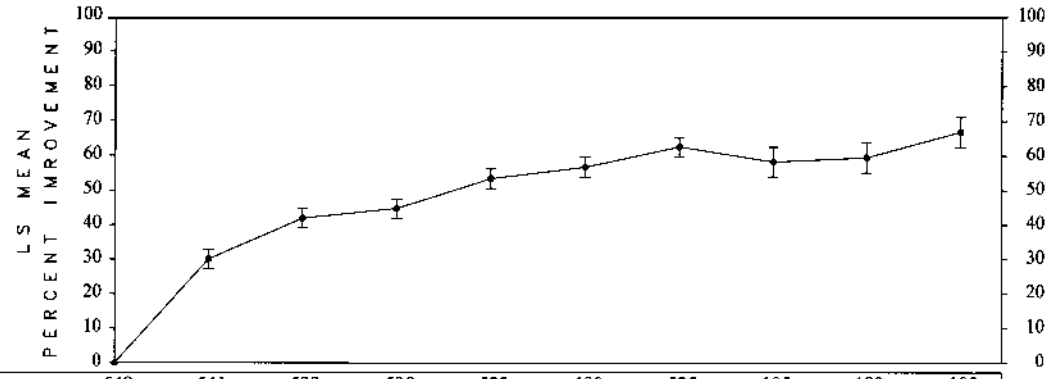


N in group	551	544	538	541	524	495	527	196	184	193
Mean % Improvement		29.6	40.5	40.1	49.7	46.9	55.4	47.9	46.3	62.9
SE of Mean % Improvement		1.78	1.72	1.94	1.96	2.16	2.39	3.66	3.83	2.59
LS Mean % Improvement (c)		29.8	40.8	40.1	49.4	46.7	55.4	46.5	44.2	61.4
SE of LS Mean % Improvement (c)		2.05	2.06	2.05	2.08	2.11	2.07	3.00	3.08	3.02
Upper 95% Limit (c)		33.8	44.8	44.1	53.5	50.9	59.5	52.4	50.2	67.4
Lower 95% Limit (c)		25.8	36.7	36.1	45.4	42.6	51.4	40.6	38.1	55.5
p-Value (c)		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
INFUSION NUMBER	#1			#2	#3	#4		#5	#6	POST
TIMEPOINT	WEEK 0	DAY 2	WEEK 1	WEEK 2	WEEK 6	WEEK 14	WEEK 16			INF. 6

Figure 1B. Patient assessment of pain (a). Least squares (LS) mean percentage improvement (b) from baseline in patients who received at least one infusion. All assessments were done prior to infusion on days of infusion. a: Score ranges from 0 to 100 with higher scores indicating greater pain. b: Percentage of improvement = 100 × (Baseline Score–Timepoint Score)/Baseline Score. c: Based on repeated measures ANCOVA model on percentage of improvement with factors for center and time and baseline as covariate and a random effect for patient within center. Patients with baseline = 0 were excluded. P values are for testing adjusted mean = 0. P values were adjusted for repeated testing using Bonferroni procedure.

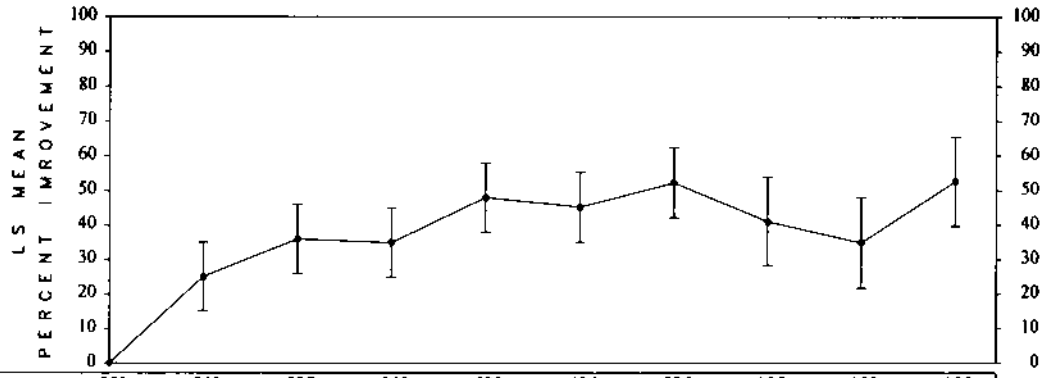
improvement from baseline (means of 18.3 and 20.4, respectively) to Week 16 (means of 7.9 and 6.6, respectively; $p < 0.001$), as displayed in Figure 2. In the subset of 197 patients who received infliximab as a 1-h infusion in the study extension, statistically significant ($p < 0.001$) improvements from baseline were maintained through 2 wks following Infusion 6 for all efficacy variables.

Adverse events. Approximately 62% of patients reported at least one adverse event at any time during the trial (Table 3). Most patients reported adverse events that were categorized



N in group	549	541	532	538	522	490	525	195	183	192
Mean % Improvement		30.1	41.9	44.9	53.8	56.9	62.6	59.8	62.0	68.8
SE of Mean % Improvement		1.24	1.36	1.45	1.45	1.61	1.80	2.24	2.47	2.44
LS Mean % Improvement (c)		30.0	41.8	44.7	53.4	56.6	62.5	58.2	59.4	66.8
SE of LS Mean % Improvement (c)		1.42	1.43	1.43	1.45	1.48	1.44	2.20	2.26	2.21
Upper 95% Limit (c)		32.8	44.6	47.5	56.2	59.5	65.4	62.5	63.9	71.2
Lower 95% Limit (c)		27.2	39.0	41.9	50.5	53.7	59.7	53.9	55.0	62.5
p-Value (c)		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
INFUSION NUMBER	#1			#2	#3	#4		#5	#6	POST
TIMEPOINT	WEEK 0	DAY 2	WEEK 1	WEEK 2	WEEK 6	WEEK 14	WEEK 16			INF. 6

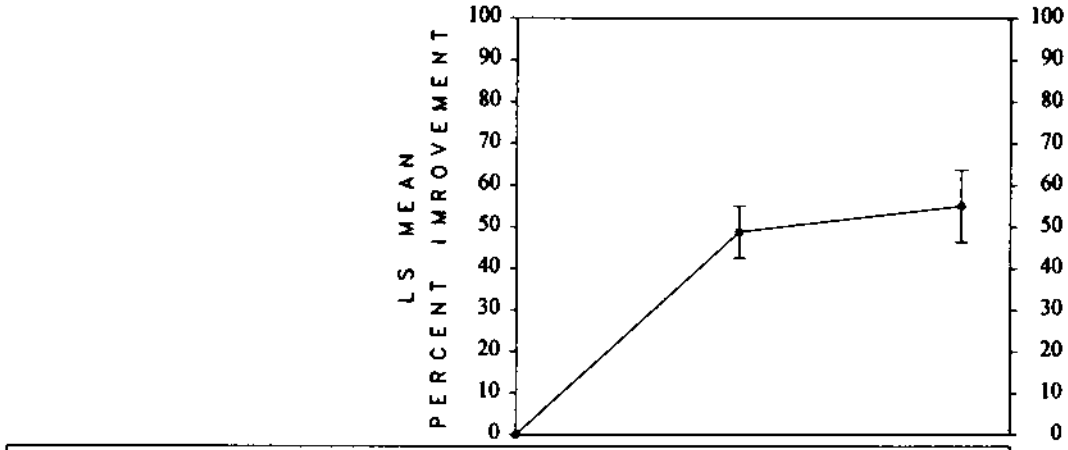
Figure 1C. Physician global assessment of arthritis (a). Least squares (LS) mean percentage improvement (b) from baseline in patients who received at least one infusion. All assessments were done prior to infusion on days of infusion. a: Score ranges from 0 to 100 with higher scores indicating severe arthritic conditions. b: Percentage of improvement = 100 × (Baseline Score–Timepoint Score)/Baseline Score. c: Based on repeated measures ANCOVA model on percentage of improvement with factors for center and time and baseline as covariate and a random effect for patient within center. Patients with baseline = 0 were excluded. P values are for testing adjusted mean = 0. P values were adjusted for repeated testing using Bonferroni procedure.



N in group	551	543	537	540	523	494	526	195	183	192
Mean % Improvement		24.6	35.4	34.9	48.2	44.8	51.9	45.8	39.6	57.5
SE of Mean % Improvement		5.22	5.56	6.80	2.89	2.69	3.93	4.18	6.31	5.26
LS Mean % Improvement (c)		25.1	35.9	35.0	47.9	45.2	52.2	41.0	34.8	52.6
SE of LS Mean % Improvement (c)		5.11	5.12	5.12	5.15	5.21	5.14	6.55	6.68	6.59
Upper 95% Limit (c)		35.1	45.9	45.0	58.0	55.4	62.3	53.8	47.9	65.5
Lower 95% Limit (c)		15.1	25.8	24.9	37.8	35.0	42.1	28.1	21.7	39.7
p-Value (c)		< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
INFUSION NUMBER	#1			#2	#3	#4		#5	#6	POST
TIMEPOINT	WEEK 0	DAY 2	WEEK 1	WEEK 2	WEEK 6	WEEK 14	WEEK 16			INF. 6

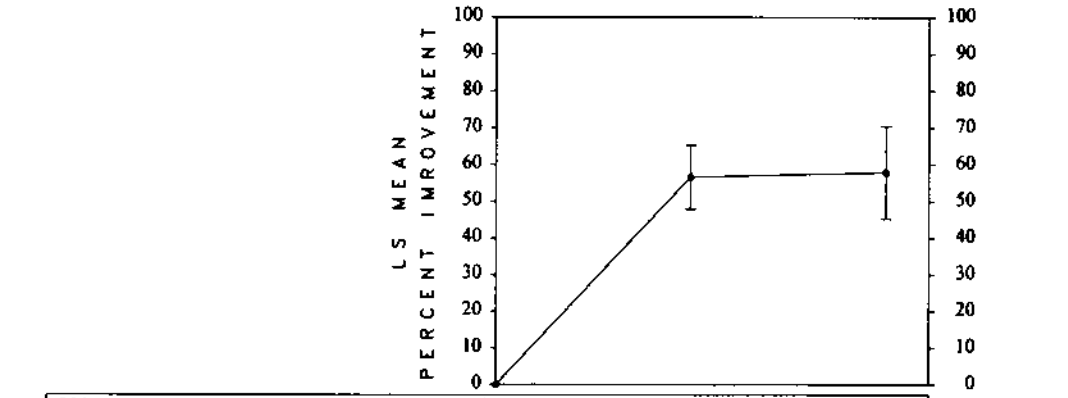
Figure 1D. Patient global assessment of arthritis (a). Least squares (LS) mean percentage improvement (b) from baseline in patients who received at least one infusion. All assessments were done prior to infusion on days of infusion. a: Score ranges from 0 to 100 with higher scores indicating severe arthritic conditions. b: Percentage of improvement = 100 × (Baseline Score–Timepoint Score)/Baseline Score. c: Based on repeated measures ANCOVA model on percentage of improvement with factors for center and time and baseline as covariate and a random effect for patient within center. Patients with baseline = 0 were excluded. P values are for testing adjusted mean = 0. P values were adjusted for repeated testing using Bonferroni procedure.

as mild or moderate in nature. Adverse events occurring in 2% or more of patients included headache (10% of patients); upper respiratory tract infection (6%); sinusitis, nausea, and fatigue (5% each); cough, dermatitis, and pruritus (4.0% each); diarrhea and nasopharyngitis (3% each); and dizziness, pyrexia, urinary tract infection, bronchitis, pneumonia, influenza, lower limb edema, sore throat, arthralgia, dyspnea, and limb pain (2% each). Among the cohort of



N in group	276	254	127
Mean % Improvement		49.8	57.7
SE of Mean % Improvement		3.36	3.74
LS Mean % Improvement (c)		48.8	55.1
SE of LS Mean % Improvement (c)		3.17	4.36
Upper 95% Limit (c)		55.1	63.7
Lower 95% Limit (c)		42.5	46.4
p-Value (c)		< 0.001	< 0.001
INFUSION NUMBER	#1		POST
TIMEPOINT	WEEK 0	WEEK 16	INF. 6

Figure 2A. Swollen joint count (a). Least squares (LS) mean percentage improvement (b) from baseline in patients who received at least one infusion. a: Swollen joint count ranges from 0 to 66. b: Percentage of improvement = 100 × (Baseline Score–Timepoint Score)/Baseline Score. c: Based on repeated measures ANCOVA model on percentage of improvement with factors for center and time and baseline as covariate and a random effect for patient within center. Patients with baseline = 0 were excluded. P values are for testing adjusted mean = 0. P values were adjusted for repeated testing using Bonferroni procedure.



N in group	273	253	127
Mean % Improvement		59.1	63.4
SE of Mean % Improvement		3.53	6.94
LS Mean % Improvement (c)		56.6	57.9
SE of LS Mean % Improvement (c)		4.38	6.37
Upper 95% Limit (c)		65.2	70.5
Lower 95% Limit (c)		47.9	45.3
p-Value (c)		< 0.001	< 0.001
INFUSION NUMBER	#1		POST
TIMEPOINT	WEEK 0	WEEK 16	INF. 6

Figure 2B. Tender joint count (a). Least squares (LS) mean percentage improvement (b) from baseline in patients who received at least one infusion. a: Tender joint count ranges from 0 to 68. b: Percentage of improvement = 100 × (Baseline Score–Timepoint Score)/Baseline Score. c: Based on repeated measures ANCOVA model on percentage of improvement with factors for center and time and baseline as covariate and a random effect for patient within center. Patients with baseline = 0 were excluded. P values are for testing adjusted mean = 0. P values were adjusted for repeated testing using Bonferroni procedure.

Table 3. Summary of adverse events (AE).

Adverse Event Summary	Number of Patients (%)		
	Overall (n = 553)	2-hr Infusion (n = 553)	1-hr Infusion (n = 197)
Patients with ≥ 1 AE			
All AE	342 (61.8)	325 (58.8)	75 (38.1)
Associated AE*	210 (38.0)	192 (34.7)	36 (18.3)
Patients with ≥ 1 serious AE			
All serious AE	47 (8.5)	40 (7.2)	9 (4.6)
Associated serious AE*	21 (3.8)	13 (2.4)	8 (4.1)
Patients with ≥ 1 AE leading to discontinuation			
All AE	36 (6.5)	27 (4.9)	9 (4.6)
Associated AE*	28 (5.1)	21 (3.8)	7 (3.6)

*Adverse events assessed by the investigator as "probable" or "uncertain."

patients receiving the 1-h infliximab infusion during the study extension, adverse events were reported by 57% of patients through Week 16, during which time infliximab was administered over 2 h, and by 38% of patients during the extension period when they received 1-h infusions of infliximab.

Approximately 8% of patients reported a total of 82 serious adverse events during the trial; approximately half of these patients (21 of 553, or 4%) experienced serious adverse events assessed by the investigator to have a probable or uncertain relationship to study drug (Table 3); all other serious adverse events were considered unrelated to study medication. The incidences of all and associated serious adverse events were similar for the 2-h and 1-h infusions. Serious adverse events reported by 2 or more patients are shown in Table 4. Two patients died during study participation. The first patient, a 62-year-old man who received 6 infliximab infusions, died 2 months after study completion as a result of pulmonary insufficiency. This patient's course was notable since approximately 2 months following the last infusion of infliximab, the patient presented with pulmonary nodules. Biopsy revealed multiple granuloma consistent with rheumatoid lung disease. The patient continued to worsen and died approximately 1 month later. After the patient's death, lung cultures became positive for *Mycobacterium tuberculosis*; this adverse event was considered to have a possible relationship to study drug by the investigator. The second patient, a 73-year-old woman who also received 6 infliximab infusions, died nearly 2 months after receiving her last infliximab infusion from complications related to a flare of chronic obstructive pulmonary disease and subsequent aspiration pneumonia. The investigator considered this patient's death unrelated to study drug administration. A third patient who received 4 infliximab infusions died of worsening congestive heart failure approximately 21 wks after receiving the last infusion of infliximab. The investigator considered this adverse event unrelated to study drug.

The incidences of all adverse events and serious adverse events were also assessed by concomitant DMARD use (MTX only vs MTX in combination with at least one other DMARD). There was no increase in the incidence of adverse events among patients who used multiple DMARD (58% of patients for all adverse events and 5% of patients with serious adverse events) relative to those receiving MTX as the only DMARD (65 and 10%, respectively).

Approximately 6% of patients were withdrawn from the study as a result of adverse events. Five patients withdrew as a result of pneumonia (all patients responded to appropriate intravenous antibiotic therapy), 4 withdrew due to hypersensitivity, 3 withdrew due to headache, and 2 patients each withdrew as a result of congestive heart failure and aggravated hypertension. Only one patient each experienced all other adverse events leading to study withdrawal. The incidences of adverse events causing withdrawal were similar for the 2-h and 1-h infusions.

Table 4. Incidence of serious adverse events (AE) reported by 2 or more patients by system-organ class for all patients.

System-organ Class* Adverse events	2–hr Infusion Data Through Week 16, n = 553 (%)	1–hr Infusion Data Study Extension, n = 197 (%)
Infections and infestations	13 (2.4)	4 (2.0)
Pneumonia	5 (0.9)	—
Gastroenteritis**	3 (0.5)	—
Immune system	—	3 (1.5)
Hypersensitivity **	—	3 (1.5)
Respiratory, thoracic and mediastinal disorders	10 (1.8)	3 (1.5)
Dyspnea**	3 (0.5)	—
Chronic obstructive airway disease exacerbated	2 (0.4)	—
Respiratory failure	—	2 (1.0)
Cardiac disorders	5 (0.9)	—
Cardiac failure, congestive	2 (0.4)	—
Musculoskeletal, connective tissue and bone disorders	5 (0.9)	1 (0.5)
Nervous system disorders	4 (0.7)	1 (0.5)
Vascular disorders	4 (0.7)	—
Venous thrombosis, deep limb	2 (0.4)	—
General disorders and administration site conditions	3 (0.5)	1 (0.5)
Chest pain	2 (0.4)	—
Injury and poisoning	3 (0.5)	—
Hip fracture	2 (0.4)	—
Gastrointestinal disorders	2 (0.4)	—
Immune system disorders	2 (0.4)	—
Reproductive system and breast disorders	2 (0.4)	—
Hepato-biliary disorders	—	1 (0.2)
Investigations	—	1 (0.5)
Metabolism and nutrition disorders	1 (0.2)	—
Psychiatric disorders	1 (0.2)	—
Renal and urinary disorders	1 (0.2)	—

* Adverse events are sorted by descending incidence within organ-system class; ** not otherwise specified

The proportions of patients experiencing infusion reactions with each infliximab infusion are shown in Table 5. The overall incidences of infusion reactions were 10% for the 2-h infusion and 6% for the 1-h infusion. The proportions of patients withdrawing from treatment due to an infusion reaction were 1% (6/553 patients) for the 2-h and 2% (4/197 patients) for the 1-h infusions. In the subset of 197 patients who received 2 additional infusions over 1 h, no increase in the frequency or severity of infusion-related adverse events was observed compared to this cohort's experience when receiving infusions over 2 h (6% of patients). Overall, the most common infusion reactions were headache (9 patients); pruritus (8 patients); urticaria (7 patients); injection site reaction (6 patients); flushing (5 patients); and hypersensitivity reaction, hypertension and injection site inflammation (4 patients each; Table 6). All of the infusion-related reactions were mild or moderate in nature, with the exception of 4 cases of severe hypersensitivity reaction (one of which was accompanied by a severe headache), one case of severe pruritus, and one case of severe anaphylactic reaction reported by a total of 6 patients (3 patients in association with the 1-h infusion and 3 with the 2-h infusion). The hypersensitivity reactions were generally characterized by facial flushing, shortness of breath, itching, erythema, rash, conjunctival infection, low back pain, throat tightness, and/or coughing. In all cases, symptoms rapidly resolved following treatment with diphenhydramine, solumedrol, and/or epinephrine. For the one patient with a reaction classified as an anaphylactic reaction, symptoms initially responded to intravenous diphenhydramine. The patient subsequently developed chills, chest heaviness, chest pain, and hypotension. Treatment with epinephrine, solumedrol, and diphenhydramine was administered. The patient was transported to the emergency department for observation and was released when fully recovered within 5 h of arrival.

The 2-h infusion was interrupted in approximately 3 to 4% of patients at Weeks 0, 2, 6, and 14. The 1-h infusion was interrupted in 5 and 2% of patients for Infusions 5 and 6, respectively. The total volume of study drug was administered in > 98% of patients for all infusions.

Table 5. Incidence of infusion reactions by infusion.

Infusion Number [Duration]	Patients (%) All Patients, n = 553	Extension Patients, n = 197
Infusion 1 [2 hr]	24 (4.3)	4 (2.0)
Infusion 2 [2 hr]	13 (2.4)	4 (2.0)
Infusion 3 [2 hr]	10 (1.9)	1 (0.5)
Infusion 4 [2 hr]	18 (3.7)	6 (3.0)
Infusion 5 [1 hr]*	—	8 (4.1)
Infusion 6 [1 hr]	—	3 (1.6)
Overall	54 (9.8)	12 (6.1)

* Note: Infusion time was decreased to 1 hr beginning with Infusion 5.

DISCUSSION

DMARD are the current standard agents for RA therapy and typically include MTX, hydroxychloroquine, leflunomide, sulfasalazine, injectable or oral gold, or azathioprine. All DMARD are relatively slow acting, taking from 1 to 6 months for initial onset of clinical response. In addition, responses to DMARD vary from patient to patient, with one-third of patients exhibiting no clinical response to therapy. Using standard therapeutic approaches, rheumatologists are not able to achieve important benefit more rapidly without resorting to glucocorticoids and exposing their patients to the associated myriad of side effects of these agents[6]. Since individuals with RA who work or manage a household may experience a marked diminution in quality of life and functional ability, more rapid onset of action could greatly alter the short-term quality of life, patient function, and lost productivity associated with RA[7].

As this was an open study, efficacy results are inevitably biased and results must be interpreted as only suggestive. In this light, infliximab treatment appeared to have a rapid onset of effect, with a 25 to 34% reduction in some of the signs and symptoms of RA by 48 h following the first infusion. Specifically, significant improvement was observed within 48 h in morning stiffness, physician's global disease assessment, patient's global disease assessment, and patient's pain assessment scores. Additional clinical benefit accrued by Week 16 and was maintained through the end of study participation. According to the study protocol, the first followup tender and swollen joint count assessment occurred 16 weeks following the first infusion. While these variables showed significant improvement from baseline to Week 16, the study design is flawed by the lack of earlier followup of these variables.

MTX is generally considered to be the standard treatment for RA in the United States; however, this agent does not halt the underlying disease process. Thus, the risk for further joint damage remains. In comparison, TNF-α inhibitors such as infliximab are associated with greater improvements in the signs and symptoms of RA and importantly, a lower risk of joint damage[1,2,8,9]. Infliximab has properties that make it appropriate for rapidly alleviating the inflammatory process of RA. First, infliximab is a potent anti-TNF-α agent able to bind cell surface TNF-α, soluble TNF-α, and TNF-α that has engaged receptors on target cells[10,11]. Since it is given as an infusion, a bolus of infliximab is delivered, resulting in rapid peak drug concentrations and expeditious TNF-α blockade.

In this trial, infliximab was administered in the outpatient setting by 97% of the participating centers. The 2-h infusion was interrupted in 3 to 4% of patients, and the 1-h infusion was interrupted in 2 to 5% of patients. The total volume of study drug was administered in > 98% of patients for all infusions. Infusion reactions were uncommon, occurring less than 5% of the time with any given infusion. This is

Table 6. Details of infusion reactions by patient.

Adverse Event Term	Duration	Severity	Serious	Caused Withdrawal From Study	Treatment Documented
Anaphylactic reaction	1d*	Severe	1 case	1 case	Diphenhydramine epinephrine, methylprednisolone
Blood pressure decreased	1h–6 h*	Moderate	No	No	None
Blood pressure increased	1h	Mild	No	No	None
Carbohydrate craving	ongoing	Mild	No	No	None
Chest tightness	1h	Mild	No	No	Diphenhydramine
Cough	5 h	Mild	No	No	Robitussin
Dizziness	1h–4h	Mild	No	No	None
Dry skin	ongoing	Mild	No	No	None
Ear pressure	1h	Mild	No	No	None
Ecchymosis	1d–3d	Mild	No	No	None
Edema	8h	Moderate	No	No	None
Fatigue	2d–6d	Mild–moderate	No	No	None
Flushing	1h–6h	Mild–moderate	No	1 case	None
Gastroenteritis	8h	Moderate	No	No	None
Gastroesophageal reflux disease	ongoing	Moderate	No	1 case	None
Headache	1h–16d	Mild-severe	1 case	No	Acetaminophen
Heart rate increased	1h	Mild	No	No	None
Hypersensitivity reaction	1h–1d	Severe	4 cases	4 cases	Acetaminophen, diphenhydramine, ethylnorepinephrine, oxygen
Hypertension	1h–12h	Mild–moderate	No	2 cases	Diphenhydramine, nifedipine, dyazide
Hypotension	2h	Mild–moderate	No	1 case	None
Injection site reaction	1h–7d	Mild–moderate	No	No	Acetaminophen, diphenhydramine
Muscle cramps	4d	Mild	No	No	None
Nausea	1 h – 5 d	Mild	No	No	None
Pain	2 h	Mild	No	No	Acetaminophen
Phlebitis	7 d	Mild	No	No	None
Pruritus	1h–1d	Mild–severe	No	No	Acetaminophen, diphenhydramine, betamethasone
Pyrexia	2h–22h	Mild	No	No	None
Rash/Dermatitis	1h–ongoing	Mild–moderate	No	No	None
Rigors	1h–4h	Mild	No	No	None
Somnolence	1h	Mild	No	No	None
Taste disturbance	6 h	Mild	No	No	None
Thirst	1 h	Mild	No	no	None
Throat irritation/tightness	1 h – 3 h	Mild	No	No	Diphenhydramine, acetaminophen
Tonsillitis	ongoing	Moderate	No	1 case	None
Urticaria	1h–2d	Mild–moderate	No	No	Acetaminophen, betamethasone diphenhydramine
Vasovagal attack	1h	Moderate	No	No	None
Vision blurred	1h–3h	Mild	No	No	None

* d: day; h: hour.

consistent with other clinical trial experience for infliximab[12]. Infusion reactions that lead to anaphylaxis are rare, occurring in less than 0.1% of infliximab infusions administered to clinical trials. Nonetheless, access to appropriate therapeutic modalities is essential. At sites in this trial, these included infusible diphenhydramine, saline, solumedrol, and injectable epinephrine. In the one patient who experienced anaphylaxis in the PROMPT study, symptoms were

recognized promptly and management was initiated immediately. This experience is consistent with that observed in clinical trials and commercial experience with infliximab.

The most common of the adverse events associated with the infusion procedure were headache, pruritus, and urticaria. The vast majority of infusion-related reactions were mild or moderate in nature, regardless of whether a 2-h or 1-h infusion period was employed. These findings parallel those obtained from an integrated safely database derived from other infliximab clinical trials in patients with RA and Crohn's disease, Overall in these studies, approximately 0.5% of infusions were associated with a serious reaction and less than 2% of patients discontinued infliximab because of infusion reactions[12].

The development of a case of tuberculosis is a cause for concern. Since becoming widely available in 1998 approximately 170,000 patients have received infliximab and 84 cases of tuberculosis have been reported (50 patients with RA, 20 with Crohn's disease, 8 with other diagnoses, and 6 with unknown diagnoses; 20 of these patients reside in the US). Thus, despite the absence of controlled data, it appears there may be an association between infliximab treatment and reactivation of tuberculosis. This potential is consistent with the putative biological activity of TNF in controlling intracellular pathogens. Accordingly, physicians who prescribe infliximab should carefully screen patients for exposure to tuberculosis and avoid therapy in high-risk individuals.

Infliximab is indicated for the treatment of RA in combination with MTX. The use of other DMARD in addition to the infliximab/MTX combination has not previously been documented in a clinical trial of patients with RA. In Crohn's disease, infliximab has been used both as monotherapy and in combination with azathioprine or 6-mercaptopurine with comparable safety and efficacy[13]. In this trial, DMARD used in conjunction with infliximab and MTX included hydroxychloroquine, sulfasalazine, and leflunomide (Table 2). There was no increase in the incidence of adverse events or serious adverse events in patients receiving DMARD other than MTX as compared to patients receiving MTX only. While the number of patients receiving a DMARD in addition to MTX is only 34% of the total population in this trial, these combinations appear to be well tolerated.

Evidence suggests that the degree of inflammatory burden correlates with overall pain, disease severity, and loss of function[14]. Since high concentrations of infliximab are achieved within 1 h after the first infusion, and subsequent infusions at 2 and 6 weeks maintain these high levels[15], the inflammatory components of the immune system responsive to TNF-α blockade are rapidly down regulated. Additionally, infliximab may theoretically unbind TNF-α that is engaged by target cell receptors[11]. Consequently, treatment with infliximab may be able to terminate target cell signaling in cells already in the process of being recruited.

In this open evaluation of 553 patients, there is some suggestion that infliximab may result in a rapid response in selected symptoms of RA. The route of administration and mechanism of action of infliximab may explain this rapid benefit as compared to alternative therapies. In addition, the ease and safety with which infliximab can be administered in the office setting over 1 or 2 h allows the rheumatologist to maintain direct supervision over the patient's treatment.

APPENDIX

The PROMPT Study Group: C. Arkin, Mid South Clinical Research, Memphis, TN; Weiss, Arthritis Consultants, Inc., St. Louis, MO; M. Berry, Nap, Bakersfield, CA; J. Arthur, McBride Clinic, Oklahoma City, OK; D. Bong, The Vancouver Clinic, Inc., PS, Vancouver, WA; F. Burch, Nap, San Antonio, TX; C. Codding, Health Advance Institute, Oklahoma City, OK; D. Cooley, Mid-America Rheumatology Consultants, Overland Park, KS; M. Eagan, Hawthorne Medical Associates, North Dartmouth, MA; J. Forstot, Rheumatology Assoc. of South Florida, Boca Raton, FL; A. Goldman, Rheumatic Disease Center, Milwaukee, WI; W. Greth, Clinical Research Center of Reading, LLP, West Reading, PA; J. Hague, Rheumatology Associates, PC, Indianapolis, IN; J. Halla, Nap, Abilene, TX; K. Riordan, CentraCare Clinic, St. Cloud, MN; J. Harshbarger, Carolina Arthritis Associates, PA, Wilmington, NC; L. Houk, Cincinnati Arthritis Associates, Cincinnati, OH; C. Huebner, Nisus Research, Petosky, MI; I.R. Isern, Nap, Beaumont, TX; L. Jacobs, Nap, Tulsa, OK; M Keller, San Diego Arthritis & Osteoporosis Med. Clinic, San Diego, CA; R. Kimelheim, Elite Medical Research, Sellersville, PA; A. Kivitz, Altoona Center for Clinical Research, Altoona, PA; J. Lawson, Medical Center at St. Francis, Greenville, SC; R. Lidman, Center for Arthritis and Rheumatic Diseases, Norfolk, VA; D. Mandel, Jefferson Park, Mayfield Village, OH; R. Marcus, Rheumatology Associates of North Jersey, PA, Teaneck, NJ; S. Maestrello, Virginia Physicians, Inc., Richmond, VA; J. Melton III, Arthritis Center PC, Chevy Chase, MD; M. Miniter, Orthopaedic & Rheumatology Associates PC, Moline, IL; B. Mohr, Health Advance Institute, South Bend, IN; M. Oza, Arthritis & Osteoporosis Treatment Center, Orange Park, FL; M. Pick, Springfield Clinic, Springfield, IL; A. Porges, Cohen & Porges Rheumatologists LLP, Hewlett, NY; M. Prupas, Nap, Reno, NV; D. Ridley, Nap St. Paul, MN; S. Roth, Nap, Phoenix, AZ; R. Katz, Rush-Presbyterian Hospital, Chicago, IL; D.F. Hughes, Nap, Muncie, IN; P. Saxe, Arthritis Associates of South Florida, Delray Beach, FL; R. Schoen, Nap, New Haven, CT; W. Shergy, Rheumatology of North Alabama, Huntsville, AL; D. Sikes, Nap, Zephyrhills, FL; J. Smith Jr., Northwest Rheumatology, Portland, OR; J. Trice, Nap, Concord, NH; D Trotter, Aurora Health Center, Racine, WI; D. Wallace, Wallace Rheumatic Study Center, Los Angeles, CA; S. Yahia, Nap, Detroit, MI; J. Condemni, AAIR Research Center, Rochester, NY; M. D'Ambrosio, Arthritis Assoc. of Colorado Springs, Colorado Springs, CO; D. Desir, Arthritis & Osteoporosis Center, PC, Hamden, CT; J.E Huffstutter, Arthritis Associates, Chattanooga, TN; P. Wheeler, Medical Specialists of Nashville, Nashville, TN; R. Ettlinger, Cedar Medical Center, Tacoma, WA; H.A. Silverman, Arthritis Medical Center, San Diego, CA; M.I. Storch, Nap, Hillsboro, NJ; G. Bayliss, Lewis Gale Clinic, Inc., Salem, VA; J. Lieberman, Nap, Decatur, GA; P. Mease, Minor & James Medical, PLLC, Seattle, WA; S. Soloway, Nap, Vineland, NJ; N. Wei, Arthritis & Osteoporosis Center of Maryland, Frederick, MD; D. Stainbrook Jr., Nap, Columbus, OH; D. Vallance, Center for Rheumatology and Integrative Health, Ann Arbor, MI; R. Malamet, The Osteoporosis & Clinical Trials Center, Hagerstown, MD; R. Rothenberg, Marshfield, WI; N. Gaylis, Arthritis and Rheumatic Disease Specialties, Aventura, FL; G. Kunkel, Nap, Harrisburg, PA; S. Carsons, Nap, Mineola, NY; R.D. Gordon, Arthritis Regional Research Center, Mercerville, NJ; E. Spencer-Smith, Nap, Santa

Rosa, CA; K. Kolba, Nap, Santa Maria CA; J.S. Toder, Nap, Johnston, RI; D. McLain, Nap, Birmingham, AL; J. Kaine, Nap, Sarasota, FL; J. Aelion, Nap, Jackson, TN; M. Abeles Univ. of Connecticut Health Center, Farmington, CT; A. Fraser, Graves-Gilbert Clinic; Bowling Green, KY; J. Tesser, Nap, Phoenix, AZ; O. Lawless, Center for Arthritis, Immunology & Env. Disorders, Olney, MD; W. St. Clair, Due Hospital, Durham, NC.

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