Infliximab Therapy in Patients with Chronic Sarcoidosis and Pulmonary Involvement

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Rationale: **Evidence suggests that tumor necrosis factor (TNF)-α plays an important role in the pathophysiology of sarcoidosis.**
Objectives: **To assess the efficacy of infliximab in sarcoidosis.**
Methods: **A phase 2, multicenter, randomized, double-blind, placebo-controlled study was conducted in 138 patients with chronic pulmonary sarcoidosis. Patients were randomized to receive intravenous infusions of infliximab (3 or 5 mg/kg) or placebo at Weeks 0, 2, 6, 12, 18, and 24 and were followed through Week 52.**
Measurements and Main Results: **The primary endpoint was the change from baseline to Week 24 in percent of predicted FVC. Major secondary efficacy parameters included Saint George's Respiratory Questionnaire, 6-min walk distance, Borg's CR10 dyspnea score, and the proportion of Lupus Pernio Physician's Global Assessment responders for patients with facial skin involvement. Patients in the combined infliximab groups (3 and 5 mg/kg) had a mean increase of 2.5% from baseline to Week 24 in the percent of predicted FVC, compared with no change in placebo-treated patients ($p = 0.038$). No significant differences between the treatment groups were observed for any of the major secondary endpoints at Week 24. Results of *post hoc* exploratory analyses suggested that patients with more severe disease tended to benefit more from infliximab treatment.**
Conclusions: **Infliximab therapy resulted in a statistically significant improvement in % predicted FVC at Week 24. The clinical importance of this finding is not clear. The results of this Phase 2 clinical study support further evaluation of anti–TNF-α therapy in severe, chronic, symptomatic sarcoidosis.**

Keywords: clinical trial; prednisone; pulmonary function tests; tumor necrosis factor

Sarcoidosis is a systemic granulomatous disease that primarily affects the lung and lymphatic systems of the body. The etiology of the disease remains unknown (1). No agent has been approved for the treatment of sarcoidosis. The majority of patients with chronic sarcoidosis receive systemic corticosteroids, which are considered to be the standard of care. In patients whose disease requires persistent corticosteroid administration, alternate therapies, such as antimalarial, cytotoxic, and nonsteroidal antiinflammatory agents, have been used (2). Because treatment with these agents is nonspecific and has shown considerable long-term toxicity and uncertain or unproven efficacy (3, 4), there is a need for more effective and safer therapies to combat this debilitating disease.

The anti–tumor necrosis factor (TNF)-α antibody infliximab (Remicade; Centocor, Inc., Malvern, PA) binds to and neutralizes TNF-α, thereby inhibiting its action after release from pulmonary macrophages and other cells. TNF-α, along with other cytokines, is critical to the development of the noncaseating granulomas that are the hallmark of sarcoidosis (5). Because infliximab has previously been reported to be efficacious in the treatment of refractory sarcoidosis (6–8), we conducted the current multicenter, randomized, double-blind, placebo-controlled study of infliximab for the treatment of chronic sarcoidosis with pulmonary involvement. Results derived from the current study were presented at the 2005 Annual American Thoracic Society Meeting, the 2005 Annual Meeting of the European Respiratory Society, the 2005 WASOG Conference on Diffuse Lung Diseases Annual Meeting, and the 2005 Annual Meeting of the American College of Rheumatology (9–18).

METHODS

Eligible adult patients had histologically proven sarcoidosis, diagnosed at least 1 yr before screening, evidence of parenchymal disease on chest radiograph, an FVC $\geq$ 50% and $\leq$ 85% of the predicted value, and a Medical Research Council dyspnea score (19) of at least grade 1. Patients must have been treated with at least 10 mg/d of prednisone or equivalent or one or more immunosuppressants for $\geq$ 3 mo before screening. Doses of these medications had to be stable for $\geq$ 1 mo before study entry. During the study, background medication regimen and doses were to remain stable. Patients with skin or eye involvement were encouraged to participate. Major exclusion criteria included any serious infections (within 2 mo of screening) or opportunistic infections (within 6 mo of screening), class III or IV congestive heart failure, current signs and symptoms of systemic lupus erythematosus, history of malignancy within the prior 5 yr, lymphoproliferative disease, and history of treated or untreated latent tuberculosis.

This was a phase 2, multicenter, double-blind, placebo-controlled study in which patients were randomized in a 1:1:1 ratio to receive intravenous infusions of placebo, infliximab 3 mg/kg, or infliximab 5 mg/kg at Weeks 0, 2, 6, 12, 18, and 24. Patients were followed through Week 52. Centocor, Inc., provided the study agent, and infusions were to be administered over at least a 2-h period.

A total of 138 patients from 34 centers in the United States and Europe were randomized between September 30, 2003, and August 31, 2004. Institutional review boards/ethics committees at the participating sites approved the study, and patients provided written, informed consent.

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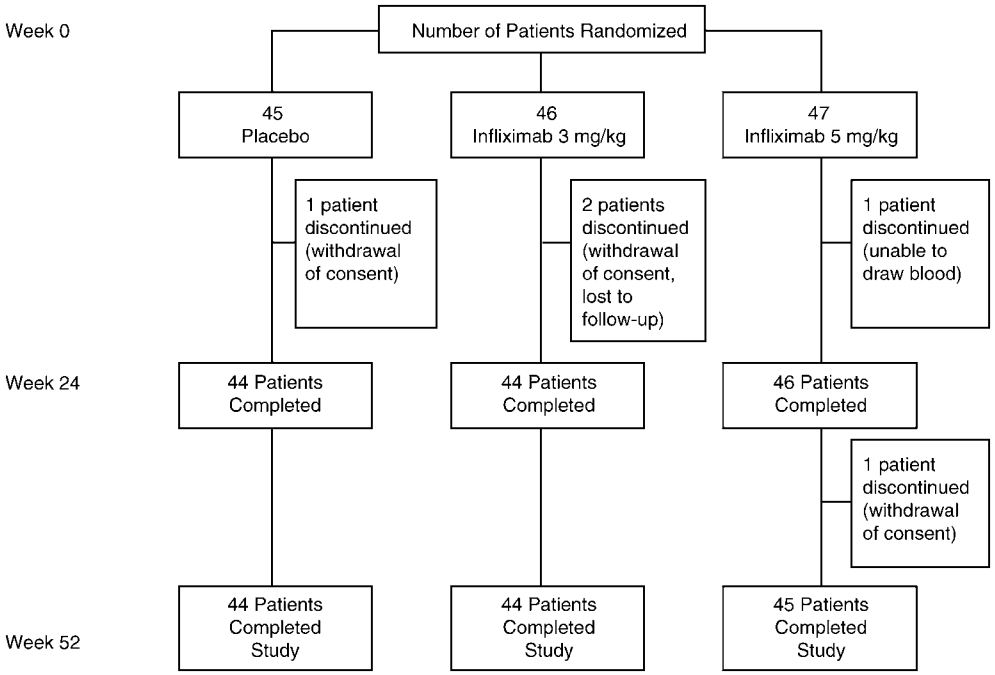

Figure 1. Patient disposition.

The primary endpoint was the change from baseline in the percent of predicted FVC at Week 24. Pulmonary function testing used a standardized calibrated laptop spirometer. Major secondary endpoints included the Saint George's Respiratory Questionnaire (SGRQ) total score (20), 6-min walk distance (6-MWD) test (21, 22), Borg's CR10 dyspnea score (before 6-MWD test) (23), and the proportion of Lupus Pernio Physician's Global Assessment (LuPGA) responders for the subset of patients with facial skin involvement at baseline.

The LuPGA, specifically developed for use in this protocol, was a semiquantitative rating scale representing the physician's assessment of the patient's lupus pernio status relative to baseline. Scores range from 6 (worsening of the patient's facial skin involvement) to 1 (100% clearing of the patient's lupus pernio). Patients with a score of 1 (clear) or 2 (excellent) were considered "responders."

Blood samples were collected for determination of serum infliximab concentrations. Serum angiotensin-converting enzyme (ACE) levels were also measured.

The chest radiograph scoring system (24) used in this study allowed quantitative comparison of chest radiographs obtained at baseline and Weeks 6 and 24. Chest radiographs were scored by two independent reviewers who remained blinded to the time point the radiograph was performed and the patient's treatment assignment. Images were evaluated for extent (score 0–4) and profusion (score 0–4) for each of four types of shadows commonly seen in sarcoidosis: reticulonodular (R), mass (M), confluent (C), and fibrosis (F).

The sample size of 40 patients per treatment group provided a statistical power of 80% to detect a 10% improvement in the primary endpoint for at least one of the infliximab groups compared with placebo. In the analysis of the primary endpoint, treatment group comparisons were made using analysis of covariance.

RESULTS

Baseline Characteristics and Patient Disposition

A total of 138 patients were randomized to treatment: 45 to placebo, 46 to infliximab (3 mg/kg), and 47 to infliximab (5 mg/kg). Two patients (one in the placebo group and one in the infliximab 3-mg/kg group) withdrew consent before administration of the first infusion of the study agent. One patient in the infliximab 5-mg/kg group withdrew consent after Week 24 but before the Week 52 visit. One hundred thirty-three (96%) patients completed the study (Figure 1).

The treatment groups were generally well balanced for baseline demographic characteristics. The infliximab 3-mg/kg group had fewer patients of African descent and a heavier average body weight compared with the other groups, but these differences were not significant ($p > 0.05$ for both comparisons). Baseline pulmonary function, symptoms, SGRQ total score, 6-MWD, and background corticosteroid doses were similar across the treatment groups (Table 1).

Change from Baseline in the Percentage of Predicted FVC

In the primary efficacy analysis, the group of patients randomized to infliximab therapy had a least squares mean increase of 2.5% from baseline to Week 24 in the percent of predicted FVC, compared with no change in the placebo group ($p = 0.038$). The mean increase in the infliximab 3-mg/kg group (2.8%, $p = 0.041$ vs. placebo) was similar to that observed in the infliximab 5-mg/kg group (2.2%, $p = 0.116$ vs. placebo; Figure 2). Response to infliximab therapy was observed as early as Week 2. The mean changes in percent of predicted FVC that were observed at Week 24 were slightly reduced through Week 52 (Figure 3).

Change from Baseline in SGRQ Total Score, Borg's CR10 Dyspnea Score (before 6-MWD), and 6-MWD

Improvement in the SGRQ total score was observed in all groups at Weeks 24 and 52, with no significant differences between the groups (Table 2). There were no significant treatment-group differences with regard to changes from baseline to Week 24 or Week 52 in Borg's CR10 dyspnea score (Table 2).

At Week 24, the least squares mean (SE) changes in 6-MWD, using last-observation-carried-forward methodology, were −5.9 (10.7), −1.7 (10.8), and 1.4 (10.6) for the placebo, infliximab 3-mg/kg, and infliximab 5-mg/kg groups, respectively. At Week 52, there was a nominally significant difference between the combined infliximab and placebo groups, with an average difference of 27.5 m ($p = 0.019$). This difference was primarily due to an average decrease (worsening) of 19.9 m from baseline in the placebo group (Table 2).

TABLE 1. BASELINE DEMOGRAPHICS, DISEASE CHARACTERISTICS, AND CONCOMITANT MEDICATIONS (RANDOMIZED PATIENTS)

Characteristics	Placebo (*n* = 45)	Infliximab, 3 mg/kg (*n* = 46)	Infliximab, 5 mg/kg (*n* = 47)	Combined Infliximab (*n* = 93)
Age	45.3 ± 9.4*	49.3 ± 9.4	46.5 ± 8.7	47.8 ± 9.1
Male, n (%)	26 (57.8)	24 (52.2)	28 (59.6)	52 (55.9)
Race, n (%)				
White	29 (64.4)	36 (78.3)	28 (59.6)	64 68.8)
Black	16 (35.6)	8 (17.4)	17 (36.2)	25 (26.9)
Asian	0 (0.0)	1 (2.2)	1 (2.1)	2 (2.2)
Other	0 (0.0)	1 (2.2)	1 (2.1)	2 (2.2)
Extrapulmonary involvement, n (%)	30 (66.7)	32 (72.7)	30 (63.8)	62 (68.1)
Years since histologically proven sarcoidosis	7.0 ± 6.2	8.0 ± 6.2	5.8 ± 6.1	6.9 ± 6.2
FVC, percent of predicted	68.8 ± 11.1	67.7 ± 9.6	69.5 ± 8.6	68.6 ± 9.1
FVC, L	2.86 ± 0.77	2.81 ± 0.86	2.84 ± 0.70	2.82 ± 0.78
FEV_1, L	1.96 ± 0.52	1.94 ± 0.65	2.02 ± 0.55	1.98 ± 0.60
St. George's Respiratory Questionnaire Total score (0–100)	45.2 ± 18.4	52.1 ± 17.3	43.3 ± 19.7	47.6 ± 19.0
6-min walk distance, m	465.3 ± 123.6	426.1 ± 115.9	467.8 ± 106.6	446.7 ± 112.7
Borg's CR10 dyspnea score (0 to > 10)	2.6 ± 2.2	2.6 ± 2.0	2.4 ± 2.0	2.5 ± 2.0
Chest radiograph R-score (0–4)	3.86 ± 4.11	3.11 ± 3.79	4.12 ± 4.34	3.63 ± 4.09
Serum angiotensin-converting enzyme (normal range = 9–67 IU/L)	43.6 ± 28.3	50.8 ± 46.8	47.7 ± 30.4	49.2 ± 38.9
Concomitant, n (%)				
Corticosteroids only	26 (57.8)	20 (43.5)	24 (51.1)	44 (47.3)
Immunomodulator only	2 (4.4)	4 (8.7)	4 (8.5)	8 (8.6)
Corticosteroid + immunomodulator	17 (37.8)	22 (47.8)	19 (40.4)	41 (44.1)
Corticosteroid dose, mg prednisone equivalent per day	13.9 ± 9.3	11.7 ± 6.9	12.2 ± 5.6	11.9 ± 6.2

Values are mean ± SD unless otherwise noted.

Proportion of LuPGA Responders and Patients with Extrapulmonary Involvement

Nineteen of the randomized patients presented with facial skin involvement (lupus pernio) at baseline. Two patients assigned to the infliximab group did not receive any infliximab treatment. Classifying these two patients who had missing data for Week 24 as nonresponders, there was one responder in the placebo group, no responders in the infliximab 3 mg/kg group, and four responders in the infliximab 5-mg/kg group (p = not significant). Exclusion of the missing Week 24 data did not alter these findings. Similar results were observed at Week 52.

The proportions of patients with extrapulmonary involvement at baseline were similar between the placebo (66.7%) and combined infliximab (68.1%) groups (*see* Table 1). By Week 24, 59.1 and 57.3% of patients in the placebo and combined infliximab groups had extrapulmonary involvement.

Chest Radiograph Scores

Reticulonodular opacities, as measured by the R-score, improved in patients in the infliximab 3-mg/kg and infliximab 5-mg/kg groups by Week 6 ($p < 0.05$); this improvement was maintained at Week 24 when compared with that of placebo (Table 2). Overall, infliximab treatment resulted in an approximate 1-point improvement, representing an approximate 26% decrease in the extent of reticulonodular infiltrates. No significant changes occurred in any of the other scores assessed (i.e., C, M, and F scores). Chest radiographs were not obtained after Week 24.

Serum Infliximab Concentrations and ACE Levels

Serum infliximab concentrations increased in a dose-dependent manner after infliximab 3-mg/kg or infliximab 5-mg/kg infusions

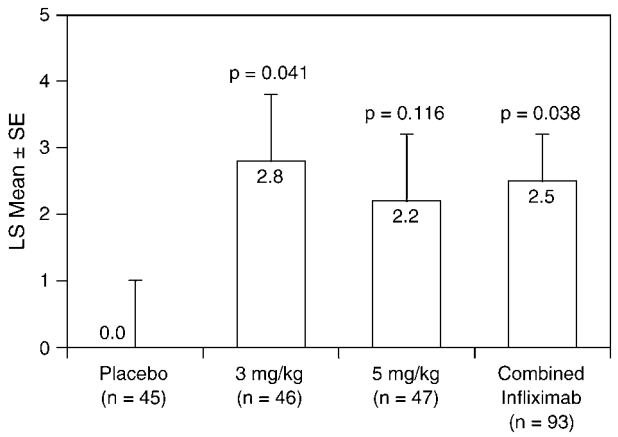

Figure 2. Summary of change from baseline to Week 24 in percent of predicted FVC with last observation carried forward. LS mean = least square mean.

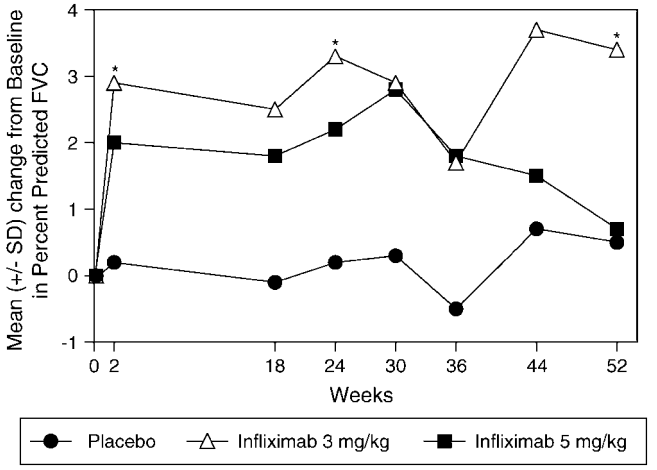

Figure 3. Mean (± SD) changes from baseline in percentage of predicted FVC through Week 52 (randomized patients, no imputation for missing data). *$p < 0.05$ versus placebo group.

TABLE 2. CHANGE FROM BASELINE IN SECONDARY EFFICACY PARAMETERS

Characteristics	Placebo (*n* = 45)	Infliximab, 3 mg/kg (*n* = 46)	Infliximab, 5 mg/kg (*n* = 47)	Combined Infliximab (*n* = 93)
SGRG total score (0–100)*†				
Week 24‡	−4.5 ± 2.1	−3.2 ± 2.2	−4.1 ± 2.1	−3.7 ± 1.5
Week 52	−2.4 ± 2.1	−2.9 ± 2.2	−3.4 ± 2.1	−3.1 ± 1.6
6-MWD, m§		−1.7 ± 10.8		−0.2 ± 7.8
Week 24‡	−5.9 ± 10.7	17.1 ± 9.4	1.4 ± 10.6	7.6 ± 6.6
Week 52	−19.9 ± 9.4	p = 0.007	−1.8 ± 9.5	p = 0.019
Borg's CR10 dyspnea score (before 6-MWD)				
Week 24	0.2 ± 2.0	0.1 ± 1.2	−0.2 ± 2.2	−0.1 ± 1.8
Week 52	0.7 ± 2.4	0.5 ± 2.2	0.1 ± 2.1	0.3 ± 2.1
Chest radiograph R-score				
Week 6	0.17 ± 1.58	−0.84 ± 1.63	−0.90 ± 2.90	−0.87 ± 2.36
		p = 0.002	p = 0.008	p < 0.001
Week 24	0.29 ± 2.21	−1.04 ± 2.02	−0.85 ± 3.62	−0.94 ± 2.93
		p = 0.001	p = 0.016	p = 0.001
Serum angiotensin-converting enzyme				
Week 12	6.9 ± 30.2	−13.2 ± 27.4	−9.8 ± 23.0	−11.5 ± 25.1
		p < 0.001	p = 0.009	p < 0.001
Week 24	7.9 ± 33.9	−13.2 ± 41.8	−9.0 ± 23.9	−11.0 ± 33.3
		p = 0.004	p = 0.013	p = 0.002
Week 52	4.6 ± 22.0	−5.3 ± 35.0	−1.2 ± 23.9	−3.1 ± 29.4
		p = 0.188	p = 0.317	p = 0.178

Definition of abbreviations: 6-MWD = 6-min walk distance; SGRQ = St. George's Respiratory Questionnaire.
Nonparametric analysis, randomized patients, p values computed based on analysis of covariance.
* Values are least squares mean ± SE for SGRQ and 6-MWD.
† Lower scores indicated better health-related quality of life.
‡ Uses last observation carried forward.
§ Longer distances indicate better function.

given at 6-wk intervals (after the induction regimen at Weeks 0, 2, and 6) and reached steady state by Week 24. Median trough concentrations at Week 24 were 3.4 and 7.5 μg/ml for the infliximab 3-mg/kg and the infliximab 5-mg/kg maintenance regimens, respectively. After the last infusion of infliximab at Week 24, serum infliximab concentrations gradually declined over time, generally falling below the lower limit of quantification by Week 36 in the infliximab 3-mg/kg group and by Week 44 in the infliximab 5-mg/kg group.

When compared with the placebo group, treatment with infliximab 3 mg/kg or 5 mg/kg resulted in a reduction of serum ACE levels by Week 12; this effect was maintained through Week 24 (Table 2). Serum ACE levels returned toward baseline levels by Week 52 in both infliximab groups. Mean levels remained above baseline at Weeks 12, 24, and 52 in the placebo group.

Subgroup Analyses

Prespecified subgroup analyses, based on age, race, sex, use of immunosuppressants at baseline, and extrapulmonary involvement, were performed for the primary endpoint and major secondary endpoints. Treatment benefit did not differ significantly by any of the prespecified variables.

Post hoc exploratory analyses were performed to assess the effect of baseline percent of predicted FVC, baseline SGRQ, disease duration, and baseline Medical Research Council dyspnea score on treatment outcome. Infliximab treatment resulted in a larger improvement in percent of predicted FVC at Week 24 in patients with longer disease duration, lower FVC, higher SGRQ total score, or more symptoms (i.e., those with more severe disease; Figure 4). Infliximab therapy seemed to be more beneficial in patients receiving immunosuppressants or higher doses of corticosteroids or in those with multiorgan extrapulmonary involvement (data not shown).

Similar trends were observed in the change from baseline in the 6-MWD, whereas no such differences were noted in the change from baseline in the SGRQ total score (data not shown).

Adverse Events

The proportions of patients who had adverse events were similar across the treatment groups. Respiratory system disorders, most notably upper respiratory tract infection, coughing, dyspnea, and bronchitis, were the most commonly reported adverse events (Table 3).

Low proportions of patients discontinued the study agent due to an adverse event in the placebo (2 of 44 patients [4.5%]) and combined infliximab (5 of 91 patients [5.5%]) groups. Serious adverse events occurred in 5 of 44 (11.4%) placebo-treated patients and in 10 of 91 (11.0%) infliximab-treated patients through Week 24 (Table 3). A similar pattern was observed through Week 52. Pneumonia was the most common serious adverse event, reported in 4 of 91 (4.4%) infliximab-treated patients and in no placebo patients. One patient, a 58-yr-old woman in the infliximab 3-mg/kg group, had a squamous cell carcinoma that was diagnosed 6 wk after the fifth infusion. This patient, who had been receiving azathioprine for several years before study participation, had a skin lesion before the study started. The patient completed the safety follow-up phase, and the squamous cell carcinoma lesion was reported to have resolved. One patient who had received six infusions of infliximab 5 mg/kg had an epithelioid sarcoma that was reported approximately 9 mo after the last study infusion. The diagnosis was made after the patient presented with spinal cord compression and abdominal thrombophlebitis 2 wk earlier. The patient died of the epithelioid sarcoma approximately 3 mo after the diagnosis was made. A 62-yr-old woman in the placebo group was hospitalized for pulmonary hypertension and class IV heart failure, as categorized by New York Heart Association Functional Class. The patient died of

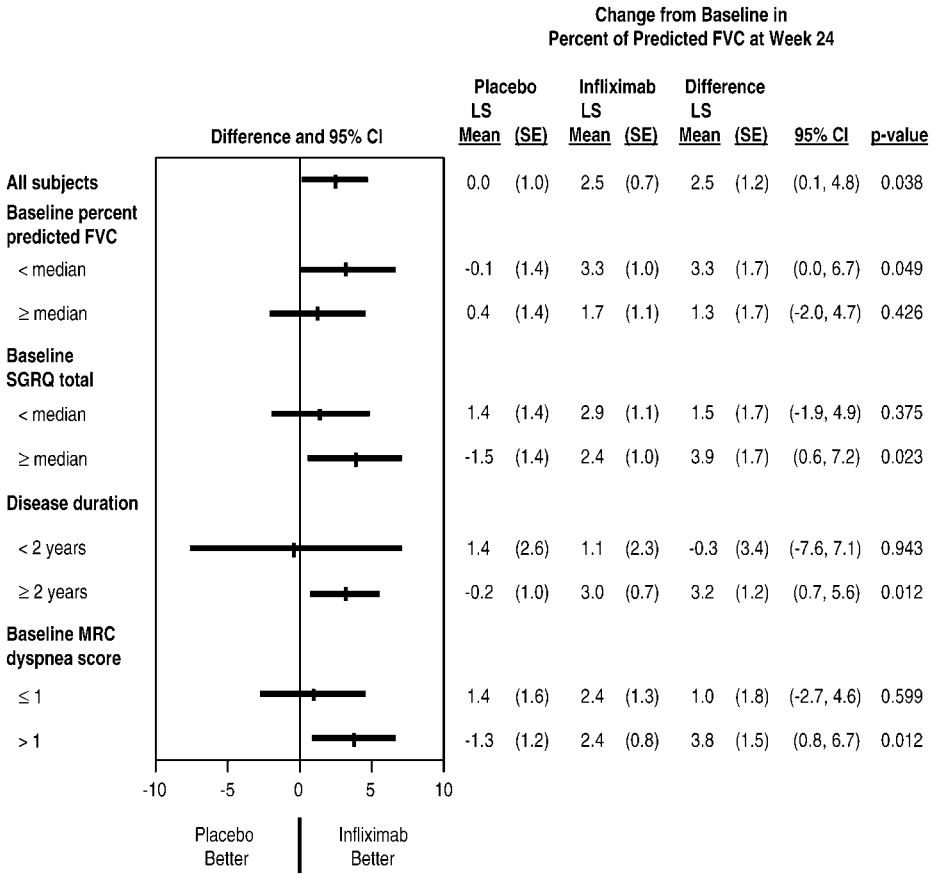

Figure 4. Summary of change from baseline in percent of predicted FVC at Week 24 by baseline percent of predicted FVC, baseline Saint George's Respiratory Questionnaire (SGRQ), disease duration, and baseline Medical Research Council dyspnea score. The median for baseline percent of predicted FVC is 69%, and the median for baseline SGRQ total score is 45.

respiratory failure secondary to progression of sarcoidosis approximately 6 wk after the last placebo infusion was administered.

Infusion reactions occurred with 2.3% of infusions in the placebo (6 of 258 infusions) and combined infliximab (12 of 529 infusions) groups. There were no anaphylactic or delayed hypersensitivity reactions reported during the study. The occurrence of infections was similar across treatment groups through Week 52 (Table 3), with the exception of pneumonia, which occurred more frequently in the infliximab 3-mg/kg (n = 3, 6.7%) and 5-mg/kg (n = 3, 6.5%) groups than in the placebo group (n = 1, 2.3%). Four of these seven pneumonia cases were simultaneously reported as serious adverse events.

DISCUSSION

Although the stimulating antigen(s) of sarcoidosis remains unknown, the alveolar macrophages in active disease have been shown to produce a variety of proinflammatory cytokines, including TNF-α, interleukin (IL)-1β, and IL-6 (25). TNF-α seems to be critical to the development of the noncaseating granulomas that are the hallmark of the disease (5). In prior case reports, therapy with the anti–TNF-α monoclonal antibody infliximab was associated with improvement of lung function in patients with refractory pulmonary sarcoidosis who had worsening lung function despite high doses of corticosteroids and other immunosuppressants (7, 26, 27).

This study is the first randomized, double-blind, placebo-controlled, clinical study to demonstrate statistically significant improvement in lung function in patients with symptomatic pulmonary sarcoidosis who were receiving infliximab in addition to stable doses of background corticosteroid and/or immunosuppressive therapy. The improvement in percent of predicted FVC was 2.5% in the combined infliximab group. This improvement in FVC was similar in magnitude to that reported with corticosteroid therapy alone for acute pulmonary sarcoidosis (28, 29). The clinical importance of the 2.5% improvement in FVC is unclear, particularly because there was no treatment benefit demonstrated by the other major secondary clinical endpoints.

Patients were required to continue on the same stable background therapy throughout the study that they had been receiving at baseline. Therefore, only patients with stable disease were eligible for participation. The stability of the disease in the study population was confirmed by the finding that the FVC in the placebo group did not change during the 24-wk treatment period. By studying patients with stable disease, background therapy may have diminished the response to infliximab therapy. In addition, exploratory analyses revealed that patients with more severe disease were more likely to benefit from infliximab therapy as measured by FVC and 6-MWD. Thus, future evaluation of anti–TNF-α therapy in sarcoidosis should focus on patients more apt to benefit from such therapy (i.e., patients with unstable or more severe disease).

Improvement in chest radiographs has been noted with corticosteroid therapy (30). In the current study, an improvement in the reticulonodular pattern was demonstrated with infliximab therapy. Improvement was not noted in the other chest radiograph scores assessed, including the M, C, and F scores.

Variations in the serum ACE level have been associated with disease activity in patients with sarcoidosis (31, 32). Corticosteroid therapy has also been associated with decreases in serum ACE levels (33, 34). Dosages of corticosteroids in the current study were stable throughout the observation period. Thus, the observed decrease in serum ACE level suggests an actual decrease in disease activity resulting from infliximab therapy.

TABLE 3. SUMMARY OF ADVERSE EVENT DATA (ALL TREATED PATIENTS)

	Placebo (*n* = 44)	Infliximab, 3 mg/kg (*n* = 45)	Infliximab, 5 mg/kg (*n* = 46)	Combined Infliximab (*n* = 91)
Adverse events through Week 24, n (%)	35 (79.5)	39 (86.7)	35 (76.1)	74 (81.3)
Commonly reported adverse events*				
Upper respiratory tract infection	8 (18.2)	14 (31.1)	8 (17.4)	22 (24.2)
Dyspnea	5 (11.4)	10 (22.2)	5 (10.9)	15 (16.5)
Pain	6 (13.6)	9 (20.0)	5 (10.9)	14 (15.4)
Coughing	4 (9.1)	7 (15.6)	5 (10.9)	12 (13.2)
Adverse events through Week 52, n (%)	41 (93.2)	40 (88.9)	40 (87.0)	80 (87.9)
Commonly reported adverse events*				
Upper respiratory tract infection	14 (31.8)	20 (44.4)	11 (23.9)	31 (34.1)
Coughing	6 (13.6)	16 (35.6)	8 (17.4)	24 (26.4)
Dyspnea	7 (15.9)	15 (33.3)	6 (13.0)	21 (23.1)
Pain	7 (15.9)	9 (20.0)	8 (17.4)	17 (18.7)
Sarcoidosis	5 (11.4)	6 (13.3)	7 (15.2)	13 (14.3)
Bronchitis	9 (20.5)	7 (15.6)	4 (8.7)	11 (12.1)
Headache	6 (13.6)	4 (8.9)	7 (15.2)	11 (12.1)
Back pain	2 (4.5)	2 (4.4)	8 (17.%)	10 (11.0)
Serious adverse events through Week 24, n (%)	5 (11.4)	6 (13.3)	4 (8.7)	10 (11.0)
Commonly reported serious adverse events†				
Pneumonia	0 (0.0%)	0 (0.0%)	12 (4.3%)	2 (2.2%)
Serious adverse events through Week 52, n (%)	8 (18.2)	11 (24.4)	10 (21.7)	21 (23.1)
Commonly reported serious adverse events†				
Pneumonia	0 (0.0)	1 (2.2)	3 (6.5)	4 (4.4)
Sarcoidosis	2 (4.5)	0 (0.0)	1 (2.2)	1 (1.1)
Cardiac failure	2 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths during the study, n (%)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Infusion reactions through Week 24 (per patient) n (%)	6 (13.6)	3 (6.7)	5 (10.9)	8 (8.8)
Infusion reaction through Week 24 (per infusion) n (%)	6/258 (2.3%)	3/260 (6.7%)	9/269 (3.3%)	12/529 (2.3%)
Infections through Week 52, n (%)				
All infections	32 (72.7)	29 (64.4)	25 (54.3)	54 (59.3)
Infections requiring antimicrobial treatment	27 (61.4)	26 (57.8)	23 (50.0)	49 (53.8)
Serious infections	4 (9.1)	6 (13.3)	4 (8.7)	10 (11.0)

Safety assessments were performed through Week 52. All adverse events that occurred between visits were reported. Infusion reactions were defined as any adverse event that occurred during or within 1–2 h after completing the study agent infusion.

* Defined as adverse events reported in > 15% of patients in any treatment group.

† Defined as serious adverse events reported in > 3% of patients in any treatment group.

In general, infliximab was well tolerated in this group of patients with symptomatic pulmonary sarcoidosis. One patient in the placebo group died of respiratory failure secondary to progression of sarcoidosis. A second death was reported after study completion; this patient in the infliximab 5-mg/kg group died of epithelioid sarcoma.

Although no causal relationship has been established, an increased incidence of certain types of malignancies (e.g., lymphoma) has been associated with the use of anti–TNF-α agents (35, 36). No cases of lymphoma were observed in this study. Two patients randomized to infliximab had malignancies. The patient (infliximab 3 mg/kg) who developed skin cancer had a several-year history of azathioprine therapy. The use of azathioprine in combination with other immunosuppressants has been associated with an increased occurrence of skin cancer (37, 38). Another patient (infliximab 5 mg/kg) was diagnosed with metastatic epithelioid sarcoma approximately 9 mo after the last infliximab infusion; this patient and died approximately 3 mo after completing the study. This rare soft-tissue sarcoma comprises less than 1% of sarcomas. If metastatic disease occurs, the prognosis is generally poor, with a median postmetastatic survival of 8 mo (39). TNF-α has been used with variable success as an adjunct to chemotherapy in some forms of sarcoma (40). At least one study has demonstrated some *in vitro* antiproliferative effect of TNF-α in some epithelioid sarcoma cell lines (41). Although there has been some suggestion that sarcoidosis itself is associated with an increased risk of cancer (42), other studies have not supported this notion (43).

Because the clinical presentation of sarcoidosis can mimic that of tuberculosis, tuberculosis must be ruled out in all cases of sarcoidosis (44, 45). Further, use of anti–TNF-α therapies has been associated with increased risk of tuberculosis infection and reactivation (46). Therefore, patients with cavitary (stage IV) disease or a history or current evidence of latent or active tuberculosis were excluded from the study. Because clinically significant fungal infections have been reported with the use of immunosuppressant therapies in sarcoidosis (47), patients with fungal infections were not eligible for participation. There were no cases of fungal infection, tuberculosis, or opportunistic infections reported in the study.

Pneumonia was more common in infliximab-treated patients (7%) than in those receiving placebo (2%). These findings are similar to those observed across all other infliximab clinical trials conducted in other indications (e.g., rheumatoid arthritis and Crohn's disease).

Infusion reactions have been reported as a potential reaction to the chimeric antibody component of infliximab (48, 49). In this study, infusion reactions were generally mild and occurred in similar proportions of infliximab- and placebo-treated patients.

In conclusion, although infliximab therapy was associated with a statistically significant improvement in percent of predicted FVC after 24 wk of therapy, treatment benefit was not demonstrated in endpoints such as SGRQ, 6-MWD, or Borg's CR10 dyspnea score in the overall study population. Thus, the clinical relevance of the FVC improvement remains unclear. Results of *post hoc* analyses suggest a greater benefit with infliximab

treatment in patients with more severe disease. However, because these were *post hoc* analyses, these findings must be viewed with caution and considered only as hypothesis generating. These results support further evaluation of anti–TNF-α therapy in patients with severe chronic sarcoidosis.

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