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C-Reactive protein predicts response to infliximab in patients with chronic sarcoidosis

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Abstract. *Background:* This study assessed the value of C-reactive protein as a predictor of disease severity and response to infliximab therapy in patients with chronic pulmonary sarcoidosis. *Design:* Sera were collected through week 52 from 138 patients with chronic pulmonary sarcoidosis who received placebo or infliximab in a randomized, double-blind, placebo-controlled study. We evaluated the response to therapy by baseline CRP using a dichotomous cutpoint (0.8 mg/dL) for the change from baseline in percent-predicted forced vital capacity (FVC), Saint George's Respiratory Questionnaire (SGRQ), 6-minute walk distance (6MWD), Borg's CR10 dyspnea score, and Physician Organ Assessment (POA). *Results***:** CRP was elevated in 36% of patients at baseline, and was significantly reduced by infliximab by week 2. Among patients with elevated baseline CRP, infliximab-treated patients improved significantly compared with placebo-treated patients in percent-predicted FVC (+2.5 versus −2.6%), 6MWD (+8.0 versus −34.1), Borg's CR10 dyspnea score (pre-6MWD −0.8 versus +0.9, post-6MWD −1.1 versus +0.8), and POA (−3.1 versus −0.3). Patients with lower CRP levels at baseline did not show significant differences between the placebo and infliximab groups in most endpoints evaluated. *Conclusions:* In chronic sarcoidosis patients, elevated CRP appears to identify a subset with more severe disease who may respond better to treatment with infliximab. *(Sarcoidosis Vasc Diffuse Lung Dis 2010; 27: 49-56)*

Key words: C-reactive protein, sarcoidosis, infliximab, forced vital capacity, 3-minute walk distance, Saint George's Respiratory Questionnaire

Introduction

Sarcoidosis is a systemic, inflammatory, granulomatous disease of unknown etiology primarily affecting the lungs and lymphatic system (1). Pulmonary involvement occurs in over 90% of patients with sarcoidosis and is the most common organ manifestation that requires systemic therapy. Extrapulmonary manifestations, while less common, may have a major impact on the prognosis and quality of life. Although sarcoidosis is a common disease with significant morbidity, the current standard of care for patients with sarcoidosis is not standardized and no FDA approved disease-specific treatments are available.

Release of tumor necrosis factor alpha (TNFα) by alveolar macrophages retrieved via bronchoalveolar lavage (BAL) is elevated in some patients with sarcoidosis and plays a key role in maintaining granulomatous inflammation. Spontaneous TNFα release by alveolar macrophages has been associated with disease progression in sarcoid patients who

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were not receiving therapy at the time of lavage (1). Inhibition of TNFα has been shown to improve symptoms in patients with sarcoidosis (2, 3). Data from several case series suggest that infliximab, a chimeric monoclonal antibody against TNFα, is safe and effective in the treatment of patients with pulmonary and refractory extrapulmonary sarcoidosis (4, 5). In a phase II, randomized, double-blind, placebo-controlled study of infliximab in patients with chronic pulmonary sarcoidosis, infliximab therapy was associated with a modest improvement in forced vital capacity, on top of background corticosteroid and/or immunomodulator therapy (6), and in extrapulmonary disease as assessed by a physician organ assessment tool (7). A post-hoc analysis suggested that study patients with more severe disease tended to benefit more from infliximab therapy (6).

C-reactive protein (CRP) is secreted in response to various inflammatory cytokines and is frequently used as a marker of inflammation. Elevated serum CRP concentration has been shown to be a significant predictor of major clinical response in patients with ankylosing spondylitis treated with the TNFα inhibitors infliximab and etanercept (8). A similar correlation between higher baseline CRP concentration and clinical response to infliximab therapy has been reported for psoriatic arthritis (9). In a large, randomized, controlled trial of combination therapy with infliximab and methotrexate for early rheumatoid arthritis, high baseline CRP was significantly correlated with joint damage progression in patients treated with methotrexate but had little impact on radiographic progression in patients treated with an infliximab-methotrexate combination (10).

Although serum CRP levels are elevated in approximately 40% of sarcoidosis patients (11), the value of CRP in predicting response to treatment with infliximab is unknown. The objective of this analysis is to evaluate the utility of baseline serum CRP concentration as a predictor of the response to infliximab therapy in patients with chronic pulmonary sarcoidosis.

Patients and methods

This was a post-hoc analysis of a phase II, randomized, double-blind, placebo-controlled study of infliximab in 138 patients with chronic pulmonary sarcoidosis at 34 sites in the United States and Europe. Sera used in this analysis were collected prospectively from all patients at weeks 0, 2, 6, 12, 18, 24, 30, 36, 44 and 52. Samples were analyzed with a standard CRP assay at a central laboratory (Quintiles Laboratories Limited, Smyrna, GA, USA). The lower limit of detection of serum CRP during the study was 0.3-0.4 mg/dL, with an upper limit of normal at 0.6 mg/dL. A dichotomous threshold value of greater than twice the lower limit of detection (i.e., >0.8 mg/dL vs. δ 0.8 mg/dL) was chosen prospectively for this analysis.

Primary details of the study have been previously reported (6). Briefly, adult patients with histologically-proven sarcoidosis diagnosed ≥1 year before screening, parenchymal disease (stage II/III), 50%-85% predicted forced vital capacity (FVC), and a Medical Research Council (MRC) dyspnea score (12) Grade ≥1 who were symptomatic despite treatment with at least 10 mg/day prednisone and/or immunomodulatory therapy were eligible. Patients were randomized 1:1:1 to receive intravenous infusions of placebo or infliximab 3 or 5 mg/kg (Centocor, Inc., Malvern, PA, USA) at weeks 0, 2, 6, 12, 18, and 24. Response to treatment was defined as the change in percent-predicted FVC at week 24. Other response measures included change from baseline to week 24 in Saint George's Respiratory Questionnaire (SGRQ) total score (13), 6-minute walk distance (6MWD) (14, 15), Borg's CR10 dyspnea score (16), and the Physician Organ Assessment (POA) (7). The protocol was approved by the institutional review board or ethics committee at each study site in compliance with the Declaration of Helsinki.

Statistical Methods

Demographic variables and baseline characteristics were summarized by the arbitrarily and prospectively chosen dichotomous cutpoint of baseline serum CRP (>0.8 vs. ≤0.8 mg/dL). Simple descriptive statistics including mean, standard deviation, and median were used for continuous variables, and count and percentage were used for discrete variables. Nominal p-values based on Fisher's exact test were calculated as needed to describe the difference between the two subgroups. Spearman correlation was used to evaluate the association between se-

lected baseline measurements (including body mass index, disease duration) and baseline CRP. The Kruskal-Wallis test was used to compare CRP values at different time points.

Treatment differences of key outcome variables including changes from baseline to week 24 in percent-predicted FVC, 6MWD, SGRQ, and POA were summarized and compared within the subsets of patients by baseline CRP level. Analysis of covariance (ANCOVA) adjusted for baseline measurement of the response variable and the investigational site was used for the analysis.

Multiple cutpoints were explored to examine the appropriateness of the selected 0.8 mg/dL cutpoint. As 0.6 mg/dL was considered the upper limit of normal for the CRP data, we considered the range from 0.6 mg/dL to 2.0 mg/dL. An independent variable-adjusted, mixed-effect model was fitted for various cutpoints. The dependent variable was the change from baseline to week 24 in percent-predicted FVC. The discrete independent variables included baseline FVC (dichotomized at median), baseline SGRQ total score (dichotomized at the median), baseline MRC dyspnea score (dichotomized at the median), disease duration at baseline (dichotomized at 2 years), treatment (placebo vs. infliximab), baseline CRP (dichotomized at the specific cutpoint), and the treatment by CRP interaction. Investigational site was considered a random effect. Applying this model to all patients, CRP appeared to be an independent predictor in the range of 0.6 to 1.0 mg/dL (Table 1). Among these various cutpoints, the prospectively chosen cutpoint of 0.8 mg/dL was one of the reasonable cutpoints.

Results

Forty-nine (36%) of 138 patients (placebo n=18, infliximab n=31) had an elevated serum CRP concentration >0.8 mg/dL at baseline (range 0.9, 24.5 mg/dL). Baseline patient demographics were generally similar between placebo and infliximab groups across this cutpoint (Table 2). When evaluating all patients with a CRP >0.8 vs ≤0.8 mg/dL, we noted that this group was more often female and non-Caucasian, and generally had more severe and extensive disease as measured by multiple parameters (Table 3). We also found that baseline serum CRP concentrations correlated significantly with BMI, MRC dyspnea score, SGRQ total score, 6MWD, Borg's CR10 dyspnea score, POA, and angiotensin-converting enzyme serum concentration (Table 4).

During therapy, the median serum CRP concentrations in patients with baseline CRP >0.8 mg/dL were reduced for the two infliximab-treated groups as early as week 2 compared with placebo. Suppression of CRP serum concentrations was maintained during treatment; these differences were no longer maintained after discontinuation of therapy (Figure 1).

Among patients with elevated baseline CRP, infliximab-treated patients improved compared with placebo-treated patients in percent-predicted

Table 1. Results of the mix-effect model

Cutpoint	N		Treatment effect (Δ % predicted FVC)		CRP effect	p-value		
	Low CRP	High CRP	Low CRP	High CRP		Treatment	CRP	Interaction
0.6	72	59	0.16	5.70	-3.64	0.02	0.56	0.01
0.7	79	52	0.70	5.11	-3.57	0.02	0.27	0.07
0.8	83	48	0.96	5.11	-4.14	0.01	0.10	0.09
0.9	89	42	0.77	5.72	-5.00	0.01	0.05	0.05
1	93	38	0.70	5.92	-4.99	0.01	0.07	0.04
1.1	100	31	2.05	3.91	-2.01	0.03	0.44	0.50
1.2	107	24	2.44	2.84	-0.84	0.08	0.67	0.89
1.3	110	21	2.38	3.49	-0.59	0.07	0.98	0.73
1.4	110	21	2.38	3.49	-0.59	0.07	0.98	0.73
1.5	111	20	2.45	3.00	-0.62	0.09	0.83	0.96
1.6	114	17	2.74	1.57	1.13	0.22	0.76	0.74
1.7	117	14	2.50	3.78	2.02	0.10	0.17	0.74
1.8	119	12	2.75	1.12	4.72	0.35	0.06	0.69
1.9	121	10	2.74	2.33	4.78	0.24	0.04	0.92
2	124	7	2.91	1.71	4.67	0.37	0.11	0.82

FVC, forced vital capacity; CRP, C-reactive protein

Table 2. Baseline patient demographics and disease characteristics, stratified by baseline C-reactive protein (CRP) level

	CRP > 0.8 mg/dL		CRP ≤ 0.8 mg/dL	
	Placebo	Infliximab 3 or 5 mg/kg	Placebo	Infliximab 3 or 5 mg/kg
N	18	31	27	57
Age (years)	46.1 ± 8.3	48.2 ± 9.2	44.8 ± 10.2	47.5 ± 9.1
Male	7 (38.9)	15 (48.4)	19 (70.4)	36 (63.2)
Caucasian	8 (44.4)	14 (45.2)	21 (77.8)	46 (80.7)
Body mass index (kg/m^2)	31.2 ± 6.8	33.2 ± 7.7	29.2 ± 5.4	29.3 ± 6.2
Body mass index ≥ 30 (kg/m^2)	6 (33.3)	20 (64.5)	12 (44.4)	21 (36.8)
Disease duration (years)	9.1 ± 7.0	8.7 ± 6.4	8.6 ± 7.1	8.4 ± 6.5
Organ involvement				
Lungs only	2 (11.1)	7 (22.6)	13 (48.1)	22 (38.6)
Lungs and others	16 (88.9)	24 (77.4)	14 (51.9)	35 (61.4)
Skin involvement	5 (27.8)	6 (19.4)	0 (0.0)	5 (8.8)
Borg's CR10 dyspnea score	1.9 ± 0.7	1.7 ± 0.8	1.4 ± 0.5	1.6 ± 0.7
Concomitant medications				
Corticosteroid only	9 (50.0)	12 (38.7)	17 (63.0)	30 (52.6)
Immunomodulator only	0 (0.0)	3 (9.7)	2 (7.4)	5 (8.8)
Corticosteroid + immunomodulator	9 (50.0)	16 (51.6)	8 (29.6)	22 (38.6)
Percent-predicted FVC	66.1 ± 10.4	68.5 ± 8.8	70.7 ± 11.3	68.7 ± 9.3
SGRQ total score	51.5 ± 24.2	55.3 ± 17.4	41.0 ± 11.9	42.6 ± 18.6
6MWD (m)	393 ± 126	415 ± 94	510 ± 101	466 ± 120
Pre-6MWD Borg's score	3.5 ± 2.3	3.2 ± 2.2	2.0 ± 1.9	2.2 ± 1.8
Post-6MWD Borg's score	4.9 ± 2.9	4.4 ± 2.0	3.4 ± 2.0	3.3 ± 1.9
Physician Organ Assessment	10.6 ± 6.8	8.1 ± 4.7	5.7 ± 3.2	6.4 ± 4.2
ACE (IU/L)	48 ± 24	62 ± 49	41 ± 31	42 ± 31

Data presented as n (%) or mean ± SD unless noted otherwise.
FVC, forced vital capacity; SGRQ, Saint George's Respiratory Questionnaire; 6MWD, 6-minute walk distance; ACE, angiotensin-converting enzyme

Table 3. Correlation between demographics/disease characteristics and baseline C-reactive protein (CRP) stratum

Variable	CRP > 0.8 mg/dL (N = 49)	CRP ≤ 0.8mg/dL (N = 84)	p-value
Age (years)	47.4 ± 8.9	46.7 ± 9.5	0.772
Male	44.9	65.5	0.029
Caucasian	44.9	79.8	<0.001
Body mass index (kg/m^2)	32.4 ± 7.4	29.3 ± 5.9	0.012
Disease duration (years)	8.8 ± 6.6	8.4 ± 6.7	0.675
Skin involvement	22.4	6.0	0.011
Multi-organ involvement	81.6	58.3	0.007
MRC dyspnea score	1.8 ± 0.8	1.5 ± 0.6	0.027
Percent-predicted FVC	67.6 ± 9.4	69.3 ± 9.9	0.283
SGRQ total score	54 ± 20	42 ± 17	<0.001
6MWD (m)	480 ± 115	407 ± 106	0.001
Pre-6MWD Borg's score	3.3 ± 2.2	2.1 ± 1.9	0.003
Post-6MWD Borg's score	4.6 ± 2.4	3.4 ± 1.9	0.004
Physician Organ Assessment	9.0 ± 5.7	6.2 ± 3.9	0.003
ACE (IU/L)	57 ± 42	42 ± 31	0.010

Data presented as % or mean ± SD. P-values were obtained using the Kruskal-Wallis test for continuous variables and Fisher exact test for categorical values. MRC, Medical Research Council; other abbreviations as in Table 2

Table 4. Correlation between demographics/disease characteristics and C-reactive protein at baseline

	N	Spearman correlation	p-value
Age (years)	133	0.072	0.410
Body mass index (kg/m^2)	133	0.265	0.002
MRC dyspnea score	133	0.233	0.007
Percent-predicted FVC	133	-0.156	0.073
SGRQ total score	133	0.334	<0.001
6MWD (m)	125	-0.396	<0.001
Pre-6MWD Borg's score	133	0.185	0.033
Post-6MWD Borg's score	133	0.182	0.036
Physician Organ Assessment	133	0.281	0.001
ACE (IU/L)	120	0.269	0.003
Disease duration (years)	133	0.047	0.592

Abbreviations as in Table 3

FVC from baseline to week 24 (mean ± SE: +2.5 ± 1.1% vs. –2.6 ± 1.5%; p=0.010; Figure 2A). A higher proportion of patients achieved at least a 5% change in percent-predicted FVC from baseline to week 24 with infliximab treatment (45.2%) than with placebo (11.8%, p=0.026). Similarly among

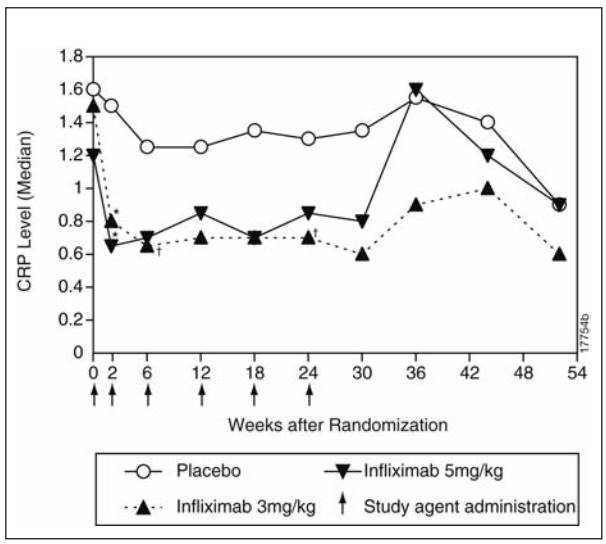

Fig. 1. Median C-reactive protein (CRP) serum levels from baseline to week 52 in patients with baseline CRP > 0.8 mg/dL
* p<0.01; † p<0.05

patients with elevated baseline CRP, those in the infliximab group improved while those in the placebo group worsened at week 24 in 6MWD (+8.0 ± 11.9 m vs. −34.1 ± 15.6 m; p=0.037; Figure 2B) and Borg's CR10 dyspnea score (pre-6MWD −0.8 ± 0.3 vs. +0.9 ± 0.4, p=0.003; post-6MWD −1.1 ± 0.3 vs. +0.8 ± 0.4, p<0.001; Figure 2C). Patients with elevated baseline CRP and infliximab treatment demonstrated significantly more improvement in POA than those treated with placebo (−3.1 ± 0.6 vs. −0.3 ± 0.8; p=0.005, Figure 2D). While placebo-treated patients demonstrated a slight 0.8 increase (i.e., worsening), infliximab-treated patients demonstrated a clinically significant 5.8 point decrease (i.e., improvement) in SGRQ total score at week 24, although this difference was not statistically significant (p=0.147).

All patients with baseline CRP ≤0.8 mg/dL tended to improve from baseline to week 24 in per-

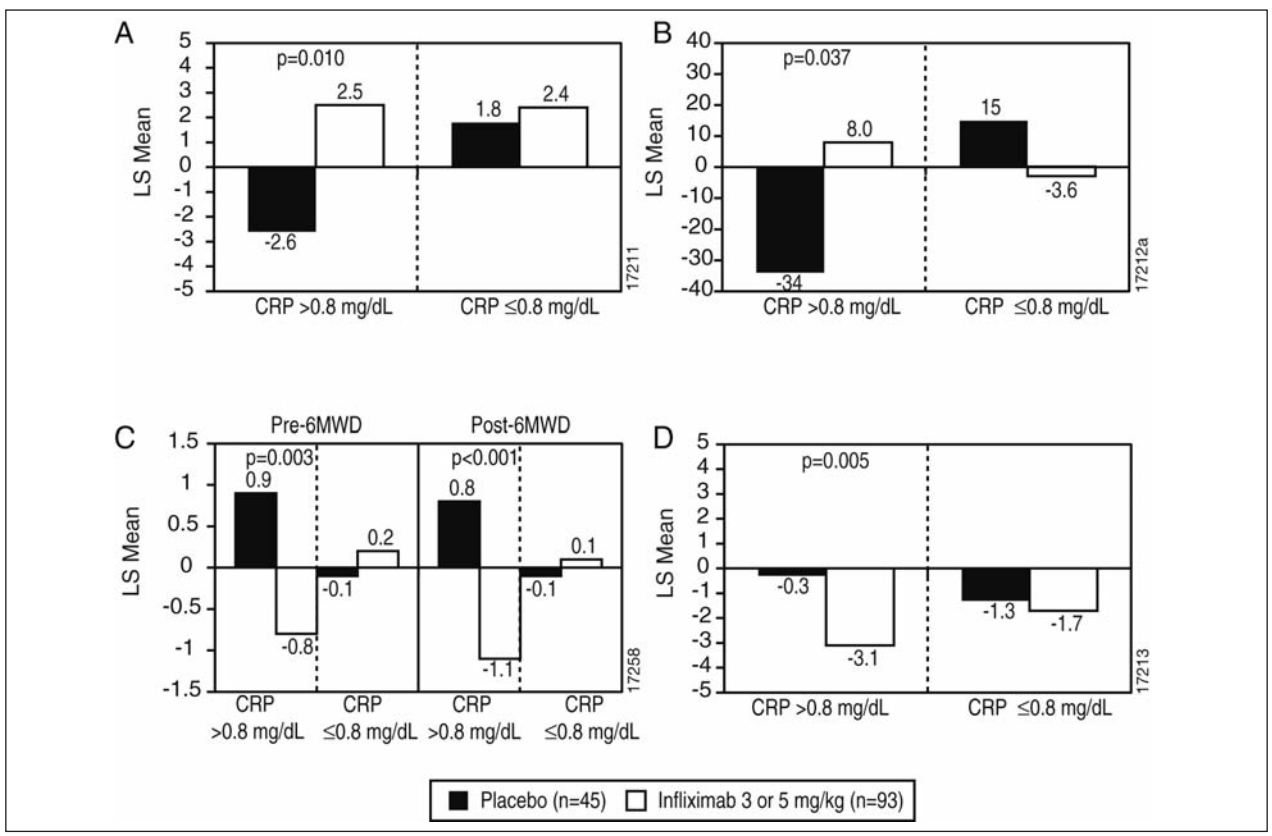

Fig. 2. Least squares (LS) mean change from baseline to week 24, by baseline serum C-reactive protein (CRP) elevation in (A) percent-predicted forced vital capacity, (B) 6-minute walk distance, (C) pre- and post-6MWD Borg's CR10 dyspnea score, and (D) physician organ assessment

Table 5. C-reactive protein (CRP) and change from baseline at week 24 in primary and major secondary endpoints

Endpoint		CRP > 0.8 mg/dL		CRP ≤ 0.8 mg/dL	
		Placebo	Infliximab 3 or 5 mg/kg	Placebo	Infliximab 3 or 5 mg/kg
Percent-predicted FVC*	Least squares mean ± SE p-value	-2.6 ± 1.5	2.5 ± 1.1 0.010	1.8 ± 1.3	2.4 ± 1.0 0.684
SGRQ total score*	Least squares mean ± SE p-value	0.8 ± 3.6	-5.8 ± 2.7 0.147	-8.2 ± 2.6	-3.0 ± 1.9 0.100
6MWD (m)*	Least squares mean ± SE p-value	-34 ± 16	8.0 ± 12 0.037	15 ± 14	-3.6 ± 9.3 0.268
Pre-6MWD Borg's CR10 dyspnea score	Least squares mean ± SE p-value	0.9 ± 0.4	-0.8 ± 0.3 0.003	-0.1 ± 0.3	0.2 ± 0.2 0.555
Post-6MWD Borg's CR10 dyspnea score	Least squares mean ± SE p-value	0.8 ± 0.4	-1.1 ± 0.3 <0.001	-0.1 ± 0.3	0.1 ± 0.2 0.611
Physician Organ Assessment	Least squares mean ± SE p-value	-0.3 ± 0.8	-3.1 ± 0.6 0.005	-1.3 ± 0.4	-1.7 ± 0.3 0.418

* Change from baseline to week 24 with last observation carried forward was used for analysis. Abbreviations as in Table 2.

cent-predicted FVC, with little difference between treatment groups (infliximab +2.4 ± 1.0%, placebo +1.8 ± 1.3%; p=0.684) (Figure 2A); similar proportions of patients achieved at least a 5% change from baseline to week 24 across the treatment groups (25.9-32.3%). No significant differences were observed in 6MWD (Figure 2B), Borg's CR10 dyspnea score (Figure 2C), POA (Figure 2D), or SGRQ total score (Table 5) between treatment groups among patients with lower baseline CRP ≤0,8 mg/dL.

Conclusions

Currently, no FDA-approved therapies exist for the treatment of sarcoidosis, although many immunomodulator therapies, including those targeting TNFα, have been tried with mixed success in treating patients with sarcoidosis (17). The randomized phase II study of infliximab in sarcoidosis achieved its primary endpoint of improvement over placebo in percent-predicted FVC, although the magnitude of the clinical result was less than had been hoped for. TNF antagonists appear to be relatively safe, especially in comparison with conventional agents. Treatment in sarcoidosis should be individualized, however, and TNFα blockade should be used with caution. Our results indicate that in this study population of chronic pulmonary sarcoidosis patients receiving corticosteroid and/or immunomodulator therapy, those with elevated serum CRP >0.8 mg/dL at baseline had more severe disease than those with lower serum CRP concentrations. We also found that most of the benefit of infliximab over placebo in improving spirometry and other associated pulmonary parameters was restricted to patients with baseline CRP >0.8 mg/dL. Although no previous studies have examined the predictive value of CRP in sarcoidosis, our results are consistent with previous studies of CRP in inflammatory arthritides (8-10).

TNFα is a key cytokine in innate immune responses and is increased in patients with sarcoidosis. TNFα has many biological effects, ranging from apoptosis to inflammation (18). Both CRP and TNFα can enhance acute inflammation and increase macrophage activation and phagocytosis (19). The most important source for TNFα in the lung is alveolar macrophages, although T cells, natural killer cells, neutrophils, and endothelial cells may also release this cytokine under certain conditions. TNFα release is upregulated in BAL cells from patients with active sarcoidosis (20-24), and elevated release of TNFα from alveolar macrophages carries a great risk of disease progression in patients with sarcoidosis (25).

The role of CRP in the initial evaluation and prediction of treatment outcomes in sarcoidosis has not been previously investigated. Serum CRP was elevated in only 30% to 40% of our patients with chronic pulmonary sarcoidosis. Baseline CRP level is a useful marker of clinical response to infliximab treatment in patients with ankylosing spondylitis; as baseline CRP and TNFα levels were higher in re-

sponders than non-responders (26). High baseline levels of CRP and interleukin-6 have been associated with clinical response to infliximab in these patients, and significant reductions in CRP, interleukin-6, and vascular endothelial growth factor have been observed following infliximab treatment (27). CRP level may also help to identify better candidates for infliximab treatment in patients with Crohn's disease (28) and psoriatic arthritis (9).

It is uncertain whether CRP is simply a useful biomarker to predict severity of disease and response to anti-TNFα therapy in sarcoidosis or whether it may also directly participate in the pathophysiology of sarcoidosis. CRP expression and release by peripheral blood mononuclear cells are enhanced by inflammatory stimuli perhaps mediated in part by Toll-like receptor (TLR) 4, NF-B, and protein kinase C (29). TNFα inhibition may down-regulate the increased expression of TLR2 and TLR4 in spondyloarthropathy (30). A highly significant association has been observed between chronic disease course and TLR4 gene polymorphisms in patients with sarcoidosis, however, no such association has been found with acute disease (31).

Our study highlights the value of CRP as a potential predictor of response to infliximab therapy in patients with chronic sarcoidosis. Our results also indicate that CRP may be an indirect measure of immune activation in a subset of sarcoidosis patients. The measurement of CRP is feasible and cost effective in most clinical settings and would enable the selection of patient populations more likely to gain clinical benefit in future clinical trials. While the CRP measurements were conducted prospectively in this patient population, our analysis was retrospective in nature and is limited by the fact that patients were not stratified by their CRP results in the study the dichotomous cutpoint was chosen arbitrarily. The mixed-effect model we developed to test the appropriateness of our arbitrary cutpoint showed that high baseline CRP, as defined by a dichotomous cutpoint at points between 0.6 and 1.0 mg/dL, is associated with greater treatment effect independently of baseline pulmonary disease severity. Above this range, the difference between groups tends to disappear. These results suggest that the selection of the actual cutpoint is less important than the finding that higher baseline levels of CRP are associated with more treatment effect. Our study also used standard rather than high sensitivity CRP assays, which might have resulted in a different cutpoint being of clinical value. Although lower CRP cutpoints have demonstrated prognostic value in cardiovascular disease, the utility of any cutpoint is highly dependent on the disease. Furthermore, the utility in guiding a pharmaceutical intervention may not be the same as a prognostic cutpoint and may not be easily generalized from one intervention to another, particularly in different diseases. Although our dichotomous cutpoint at 0.8 mg/dL has been used previously with routine CRP measurements as a predictive marker (32), it is unlikely for there to be a single best cutpoint.

In conclusion, similar to previous studies in autoimmune diseases, this study of chronic pulmonary sarcoidosis suggests that patients with elevated serum CRP levels at baseline appeared to have a greater response to infliximab therapy as measured by percent-predicted FVC, 6MWD, Borg's CR10 dyspnea score, and POA. Additional studies to confirm these results in patients with chronic sarcoidosis appear warranted.

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