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Efficacy of Infliximab in Extrapulmonary Sarcoidosis:

Results from a Randomized Trial

Marc A. Judson, M.D.[1]

Robert P. Baughman, M.D.[2]

Ulrich Costabel, M.D.[3]

Susan Flavin, M.S.N.[4]

Kim Hung Lo, Ph.D.[4]

Mani S. Kavuru, M.D.[5]

Marjolein Drent, M.D., Ph.D.[6]

And the Centocor T48 investigators[7]

1: Division of Pulmonary and Critical Medicine, Medical University of South Carolina, Charleston, South Carolina, USA
2: University of Cincinnati Medical Center, Cincinnati, Ohio, USA
3: Department of Pneumology/Allergy Ruhrlandklink Essen, Essen, Germany
4: Centocor, Inc, Malvern, PA, United States
5: Dept of Pulmonary & Critical Care Medicine, Cleveland Clinic Foundation. Cleveland, Ohio, USA
6: Department of Respiratory Medicine, Sarcoidosis Management Team, University Hospital Maastricht, Maastricht, The Netherlands
7: See Appendix 1

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Reprint requests: Marc A. Judson, M.D., Division of Pulmonary and Critical Care Medicine, 96 Jonathan Lucas Street, Charleston, South Carolina 29425
Email: judsonma@musc.edu

Abstract:

Objective: To investigate the efficacy of infliximab for the treatment of extrapulmonary sarcoidosis.

Design: Prospective, randomized, double-blind, placebo-controlled trial comparing placebo with infliximab 3 mg/kg and infliximab 5 mg/kg given over 24 weeks. Extrapulmonary organ severity was determined by a novel severity tool (extrapulmonary Physician Organ Severity Tool, or ePOST) with an adjustment for the number of organs involved (ePOSTadj).

Population: 138 enrolled in a prospective randomized trial of infliximab versus placebo for the treatment of chronic corticosteroid-dependent pulmonary sarcoidosis.

Results: Baseline severity of extrapulmonary organ involvement as measured by ePOST was similar across treatment groups. After 24 weeks of study drug therapy, the change from baseline to week 24 in ePOST for the combined infliximab group compared with the placebo group was greater ($p< 0.01$). After adjustment for the number of extrapulmonary organs involved, the improvement in ePOSTadj observed in the combined infliximab group was also greater to that observed in placebo-treated patients after 24 weeks of therapy ($p<0.05$). The improvements in ePOST and ePOSTadj were not maintained during a subsequent 24-week washout period.

Conclusions: Infliximab may be beneficial compared with placebo in the treatment of extrapulmonary sarcoidosis in patients already receiving corticosteroids as assessed by this severity tool.

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown cause. The disease may remit spontaneously or with treatment. Sarcoidosis is chronic, or progressive, in approximately 25 percent of patients. Such patients require long-term therapy to avoid progressive organ dysfunction. Corticosteroids are currently recommended as the drug of choice for sarcoidosis [1,2]. However, the cumulative toxicities of corticosteroids make their long-term use problematic. Efforts should be made to taper corticosteroids to the lowest effective dose [1].

Because of the side effects associated with long-term use of corticosteroids, there is interest in alternative therapies for sarcoidosis. Other than corticosteroids, drugs that have been studied in sarcoidosis have included methotrexate [3], hydroxychloroquine [4], azathioprine [5], and cyclophosphamide [6,7].

Recently, case reports and series have reported efficacy of tumor necrosis factor alpha (TNFα) antagonists for the treatment of pulmonary and extrapulmonary sarcoidosis [8-14]. There is a sound rationale for this therapy because TNFα is released by macrophages in patients with sarcoidosis [15], and TNFα is thought to be integrally involved in the development of the granulomatous inflammation [16]. Furthermore, sarcoidosis patients whose disease is refractory to treatment with corticosteroids tend to have high levels of TNFα in bronchoalveolar lavage fluid [17]. Because patients with extrapulmonary sarcoidosis, such as those with chronic skin, upper respiratory tract,

and neurological involvement, tend to be recalcitrant to corticosteroid therapy [6,18,19], TNFα antagonists may be especially useful in these patients.

Infliximab is a chimeric IgG monoclonal antibody directed against TNFα [20]. A randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of inflixmab for chronic corticosteroid-dependent pulmonary sarcoidosis [21]. The primary endpoint of this study was improvement in forced vital capacity (FVC) after 24 weeks of treatment. The effect of infliximab on extrapulmonary sarcoidosis organ involvement was evaluated as a secondary endpoint of this study. An extrapulmonary organ severity tool (ePOST) was developed for this evaluation. This manuscript reports the results of sarcoidosis extrapulmonary organ involvement in this trial.

Methods

Eligibility

Eligible adult patients were required to have histologically proven sarcoidosis diagnosed at least 1 year prior to screening and evidence of parenchymal disease (stage II or III) on chest radiograph. Additional eligibility criteria included an FVC $\geq$50% and $\leq$85% of the predicted value and a Medical Research Council (MRC) dyspnea score [22] of at least Grade 1. Patients were required to have been treated with at least 10 mg/day of prednisone equivalent or one or more immunosuppressants for at least 3 months prior to screening. Doses of these medications were to have been stable for at least 1 month prior to study entry. During the study, background medication regimen and doses were to remain stable.

Patients were excluded from the study if they had a history or current evidence of latent or active tuberculosis, chronic or serious infections within 2 months of screening, malignancy, or congestive heart failure. Previous administration of infliximab or other TNFα inhibitors within 3 months prior to screening excluded patients from participation.

Study design

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 either placebo, infliximab 3 mg/kg, or infliximab 5 mg/kg at weeks 0, 2, 6, 12, 18, and 24, and were followed through week 52. This design was selected to simultaneously assess a priori the efficacy of infliximab (placebo versus the combination of the 3 mg/kg and 5 mg/kg groups) as well as determine if there was a dose-response (placebo versus 3 mg/kg versus 5 mg/kg groups). Randomization was done by an interactive voice recognition system (IVRS). Subject allocation to treatment groups as performed using an adaptive stratified design with the following strata: (1) investigational site; and (2) the presence or absence of disfiguring facial sarcoidosis skin lesions (lupus pernio) as determined by the investigator. The IVRS assigned randomized subjects to a specific kit which was known to exist at the study site. Assignments were not done by block randomization but were allowed to be adjusted by a computer program to maintain balance overall using the strata noted above. Enrollment was performed by study investigators and coordinators. The first subject was consented for enrollment on September 30, 2003 and the last subject visit was September 30, 2005. Infliximab was

provided by Centocor, Inc., Malvern, PA, and infusions were to have been administered over at least a 2-hour period.

One hundred thirty-eight patients from 34 centers in the United States and Europe were randomized between 30 September 2003 and 31 August 2004. Institutional Review Boards/Ethics Committees at the participating sites approved the study, and patients provided written informed consent before any protocol-specific procedures were performed.

Efficacy and safety evaluations

The primary endpoint was the change from baseline in the percent of predicted FVC at week 24. The results of this primary endpoint are the topic of another publication [21].

The efficacy of infliximab in the treatment of extrapulmonary sarcoidosis was assessed as a secondary endpoint of this study. The definition of involvement of sarcoidosis in an extrapulmonary organ was based on a clinical decision of the principal investigator at each clinical center. The principal investigators were all experienced in the clinical presentation and management of sarcoidosis. Sarcoidosis organ assessment was performed using an extrapulmonary Physician Organ Severity Tool (ePOST) that was designed for the purpose of this study. The ePOST examined the state of sarcoidosis extrapulmonary organ involvement in 17 extrapulmonary organs (Table 1). At each visit, each of the 17 organs was evaluated by the study investigator. Investigators were instructed to use all clinical information available to them, including laboratory analyses,

and assessments by subspecialists to assess each organ system. Each organ was scored on a scale from 0 (not affected) to 6 (very severely affected; Table 2). Therefore, the ePOST score could range from 0 (0 x 17) to 102 (6 x 17). Because the ePOST score was a summation of all extrapulmonary organ involvement and was not weighted for specific organ involvement, major changes in one organ may have had their effect on the ePOST score diluted by the number of organs affected. To adjust for this potential confounding effect, an ePOSTadj score was calculated that equaled the ePOST score divided by the number of extrapulmonary organs involved at any time during the study. Although it was a secondary endpoint the scoring system for each organ was established a priori. However the ePOST was constructed post hoc in order to examine if infliximab had an effect on extrapulmonary sarcoidosis.

In an attempt to determine if the organs of the most important clinical impact were affected to a greater or lesser degree than the other organs, separate ePOST scores were calculated for “major organs” (cardiac, CNS, liver, bone marrow, renal, and eyes) and “minor organs” (bone/joint, muscle, skin, spleen, nose, peripheral lymph nodes). The remaining organs were not included because of a small number of patients who had involvement in those organs.

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 hour after completing the study agent infusion.

Statistical analyses

For the primary endpoint, treatment effect was tested using analysis of covariance (ANCOVA). The details of analysis and results were presented in a separate publication [21] and are not included in this manuscript.

As a post hoc analysis, the ePOST score, which was the sum of the severity scores for all 17 extrapulmonary organs, was summarized by visit using descriptive statistics. No formal statistical comparison was made. As part of the descriptive statistics, nominal p-values were produced based on an ANCOVA model, similar to that for the primary endpoint, for change from baseline. Descriptive statistics and nominal p-values were also produced for ePOSTadj.

Individual organ involvements were also evaluated in addition to the aggregation (i.e., ePOST). Due to the potential skewness of the data, a nonparametric test, Wilcoxon Rank Sum Test, was used to perform between treatment comparisons. Nominal p-values are provided. Since the comparisons are for descriptive purpose, no adjustment for multiple comparisons was made.

Results

Baseline characteristics

The baseline characteristics of the enrolled patients are shown in Table 3. On average, patients were 47.0 $\pm$ 9.3 years (range of 45 to 50 years), had a slight male predominance (56.5%), were approximately one-third Black (29.7%), had a history of

sarcoidosis for 6.9 ± 6.2 years, and had a baseline mean FVC of 68.7± 9.7 percent of predicted. Approximately two-thirds of patients had extrapulmonary sarcoidosis involvement (92/136, 67.6%). Two patients who were randomized did not receive any study drug and thus did not have an ePOST performed. Both of these patients were randomized to the infliximab 3-mg/kg group. The baseline clinical characteristics are comparable between the placebo and the combined infliximab groups.

Table 4 shows the proportions of study patients with extrapulmonary organ involvement at baseline. Figure 1 shows the number of extrapulmonary organs involved with sarcoidosis at baseline by treatment group. At baseline, the treatment groups were similar with regard to number of organs involved. As required by the study protocol, all patients had at least one organ, the lungs, affected. However, approximately 25% (33/136) of patients presented with two organs involved; and it was quite common (approximately 40% [53/136]) of patients overall) to have three to six organs affected.

Changes in organ involvement

The mean ePOST values over time in the placebo and combined infliximab groups are shown in Figure 2. Although the mean± SEM ePOST value at baseline was slightly higher in the placebo group (4.00 ± 0.81) than in the infliximab group (3.55 ± 0.43), the difference was within variability. The mean ± SEM ePOST values at week 24 for the combined infliximab and placebo groups were 2.09 ± 0.32 and 3.70 ± 0.85, respectively. The improvement in ePOST scores at week 24 was higher in the combined infliximab group, as well as the individual infliximab dose groups, compared with the placebo

group ($p< 0.01$ for all comparisons). The improvement in mean ePOST score was not maintained after infliximab treatment was discontinued.

Changes in organ involvement from baseline to week 24, as assessed by ePOST.are presented in Table 5. The infliximab group had had less organs involved with sarcoidosis at week 24 compared to baseline in 38% (34/89) of patients compared to only 16% (7/44) of those receiving placebo.

After adjustment for the number of extrapulmonary organs involved, the improvement noted in the ePOSTadj score observed in the combined infliximab group was also statistically significantly greater to that observed in placebo-treated patients at the week 18, 24, 30, and 44 evaluations ($p<0.05$; Figure 3).

Table 6 describes the response of individual organs to infliximab compared to placebo. Because of the small sample sizes, no meaningful conclusions could be identified. Four organs were not reported in Table 6 (throat, nose ear, and GI) because less than 5 subjects had involvement of these organs at both baseline and week 24. However in these 4 organs, the infliximab group did the same or better than the placebo group in every case. There were no substantial differences in the concomitant medications used for sarcoidosis treatment within or between groups [21]. Therefore a stratified analysis of ePOST scores was not required.

Table 7 shows the change in ePOST in two subgoups of organs, major and minor (see methods section), between week 0 and week 24. Although the change was greater in the major organs than the minor organs, it was not significant for either subgroup.

Adverse events

The adverse events of this study have been reported previously [21]. The proportions of patients who had adverse events were similar across the treatment groups. Infusion reactions occurred with 2.3% of infusions in both 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.

Discussion

This double-blind randomized study demonstrated that infliximab therapy improved extrapulmonary sarcoidosis compared to placebo as assessed by a novel severity tool, the extrapulmonary organ severity tool (ePOST). Similar findings were observed when an adjustment was made for the number of extrapulmonary organs involved (ePOSTadj). All patients in study were required to be on a stable dose of corticosteroid or another immunosuppressant to control their pulmonary sarcoidosis. Therefore the results of this trial suggest that infliximab provides additional benefit for extrapulmonary sarcoidosis beyond that achieved with standard sarcoidosis treatment.

The total score of extrapulmonary sarcoidosis severity was decreased by more than 40 percent in the infliximab groups compared with placebo after 24 weeks of therapy. The

difference between groups was not maintained after cessation of therapy at week 24. This was primarily due to the worsening in the infliximab 3-mg/kg group [21]. Although investigators were encouraged to keep the dose of any concomitant medications as consistent as possible throughout the study, some patients did undergo modifications in their concomitant medication regimen. The impact of this remains unclear. In addition, the extrapulmonary organ severity score also showed improvement in the infliximab groups compared with the placebo group when adjusted for the number of organs involved. Thus, we believe that it is appropriate to calculate the ePOSTadj score as well as the ePOST score because otherwise small changes in a few organs will be amplified in a severity score if a patient has many organs involved.

There are several potential limitations of this severity tool. First, the definition of involvement of sarcoidosis in an extrapulmonary organ was arbitrary, based on a clinical decision of the principal investigator at each clinical center. However, the principal investigators in this study were all experienced in the clinical presentation and management of sarcoidosis. Although we do not have data concerning the degree of certainty of the diagnosis of extrapulmonary organ involvement, we suspect the diagnosis is predominantly accurate, as three of the five most frequent extrapulmonary organs identified were the peripheral lymph node, skin, and eye (Table 4). The first two of these organs are most likely to be confirmed by biopsy or the presence of lupus pernio facial skin lesions, and the eye by ophthalmologic examination. These are very secure methods of diagnoses of sarcoidosis organ involvement in patients with biopsy-proven pulmonary sarcoidosis. However, detection of extrapulmonary organ

involvement was not standardized. Therefore assessment of changes in extrapulmonary organ involvement by sensitive techniques (e.g. positron emission tomography scanning) may have escaped assessment in many patients. As a second limitation, this tool has not been previously validated as reproducible or related to clinical outcome. Third, the ePOSTscore was a summation of all extrapulmonary organ involvement and did not include weighting for specific organ involvement. Thus, major changes in one organ may have been diluted by the number of organs affected. For this reason the ePOSTadj score was also calculated, which attempts to adjust for this confounding effect. Also, patients with more extensive involvement of certain organ systems might have had more supplementary information available for the physician to base their assessment upon. Additional measures to evaluate each organ system (i.e., laboratory analyses) were not mandated by the protocol, and it is possible that some physicians may have had such information available to them while others did not.

The tool also weighted each organ similarly while certain organs probably have a greater impact on clinical function and quality of life than others. For example, peripheral lymph nodes were the most common site of extrapulmonary sarcoidosis and therefore carried the most weight on this assessment system. It is very likely that other extrapulmonary organs were much more important. We therefore examined the subgroups of organs that have a potential major clinical impact (“major organs”) and those that have a minor clinical impact (“minor organs”). Subgroup analyses such as these must be viewed with extreme caution as the subgroups were formed arbitrarily and the sample sizes were less than for the entire cohort. Both subgroups

demonstrated a reduction in ePOST between week 0 and week 24. However the ePOST did not reach statistical significance in either subgroup, most probably because of the smaller sample sizes when compared to the entire cohort. In addition, problems of reproducibility and subjectivity of the tool would be likely to create statistical noise and make the tool less reliable, which would tend make the tool less likely to show differences between the placebo and infliximab groups. Nevertheless, statistical differences were noted between the placebo and infliximab groups despite these potential shortcomings. Another limitation was that the primary pulmonary study and this secondary extrapulmonary study may have suffered from a selection bias. Investigators may have opted to administer infliximab in an open label fashion to patients with severe or progressive disease thereby biasing enrollment of toward subjects with milder disease. Such a bias may have actually made it more difficult to detect significant changes from infliximab therapy, but this remains conjectural.

It should be noted that the severity of extrapulmonary sarcoidosis was a secondary endpoint of this study. Patients enrolled in this study were required to have the lung as the primary organ of sarcoidosis involvement; and although patients with extrapulmonary sarcoidosis were encouraged to participate, this was not an eligibility requirement. Thus, some patients with extrapulmonary manifestations of sarcoidosis had more organs involved than others. It is conceivable that patients with severe extrapulmonary sarcoidosis would have responded differently to infliximab. However, the fact that these patients with relatively mild extrapulmonary sarcoidosis demonstrated

a response to infliximab suggests that it might be effective with more severe extrapulmonary disease.

Another potential limitation of this study is that the duration of therapy was only 24 weeks. There appears to be a dose-dependent increase in the risk of serious infections and malignancies with anti-TNFα antibody therapy [25]. Therefore the risk-benefit ratio of infliximab therapy for extrapulmonary sarcoidosis may not have been completely assessed in this trial.

Other sarcoidosis instruments have been developed to assess the disease. A sarcoidosis assessment instrument was developed as part of the National Heart Blood and Lung study entitled “A Case Control Etiologic Study of Sarcoidosis” (ACCESS) [23]. However, this instrument was not appropriate for our study because it determines whether an organ is involved with sarcoidosis but does not assess the severity of organ involvement. Instead, the ACCESS instrument was used as a guide to define specific organ involvement. In addition, Wasfi and coworkers developed a sarcoidosis severity score [24]. That score was derived by sarcoidosis experts who subjectively graded the severity of 100 vignettes of sarcoidosis cases. The vignettes were “broken down” into objective information that they contained, and then a logistic regression analysis extracted the objective components upon which these experts scored disease severity. The resulting equation was then “validated” by three additional international sarcoidosis experts who graded these same vignettes. Although this score would have been of interest in this study, it was published after the initiation of this trial.

In conclusion, the results of the ePOST assessment performed during this randomized, double-blind, placebo-controlled study suggests that infliximab may be beneficial in the treatment of extrapulmonary sarcoidosis in patients already receiving corticosteroids. Further study of this agent and other TNFα antagonists is warranted in this group of patients.

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Figure legends

Figure 1. Bar graph of distribution of number of extrapulmonary organs involved by treatment group.

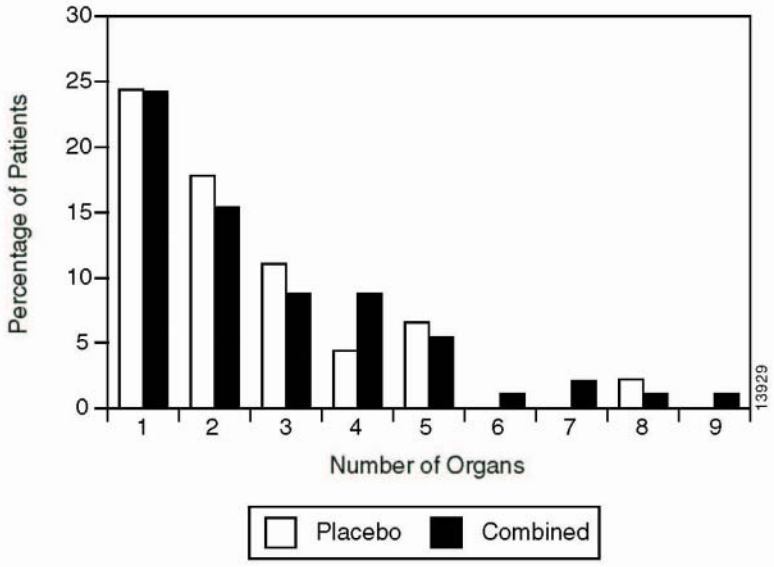

30
25
20
15
10
5
0
Percentage of Patients
1
2
3
4
5
6
7
8
9
Number of Organs
13929
Placebo
Combined

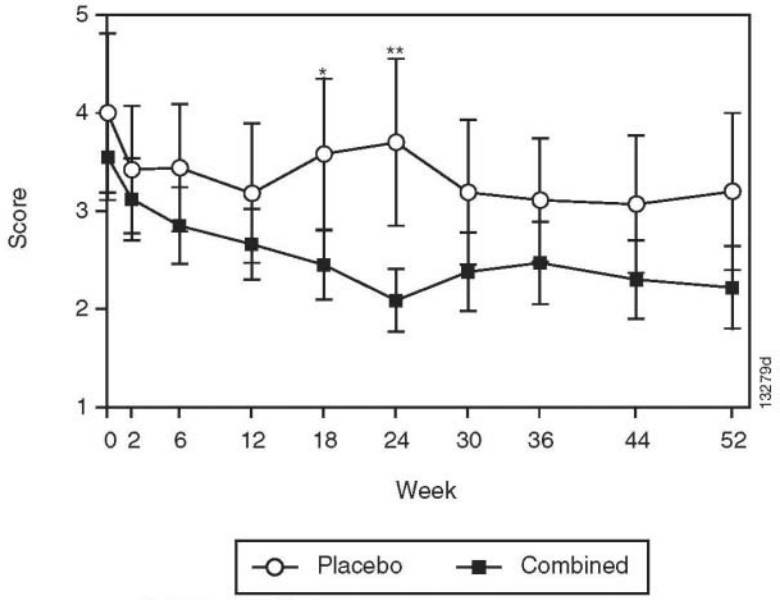
Figure 2. Mean (SE) ePOST scores at each assessment by treatment group through week 52.

$p > 0.05$ if not specified

*Combined group vs. placebo group, $p = 0.0247$

**Combined group vs. placebo group, $p = 0.0019$

**Comparisons between groups are based upon change from baseline values



p > 0.05 if not specified
*Comb vs. PBO, p = 0.0247
**Comb vs. PBO, p = 0.0019
Comparisons between groups are based upon change from baseline values

Figure 3. Mean (SE) ePOSTadj scores at each assessment by treatment group through week 52. Note that ePOSTadj = (ePOST)/(# extrapulmonary organs involved at any time during the study).

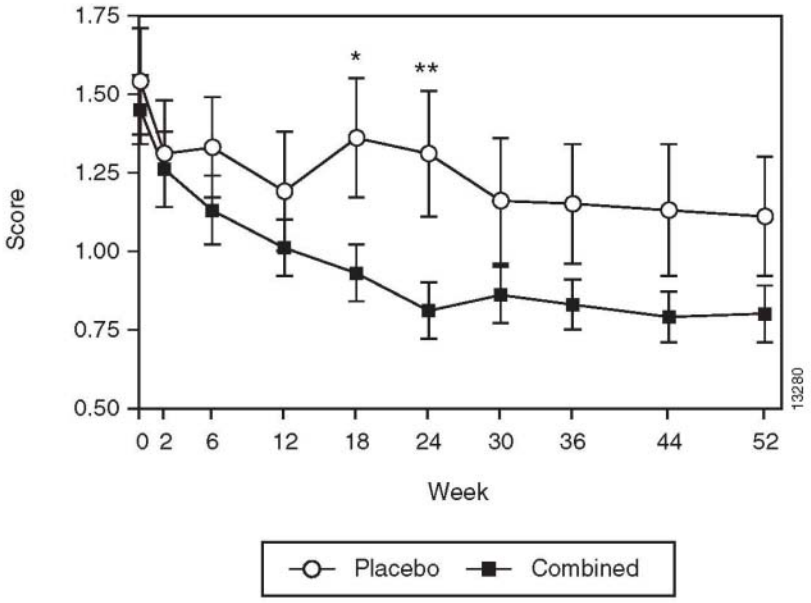

1.75
1.50
1.25
1.00
0.75
0.50
Score
*
**
0 2 6 12 18 24 30 36 44 52
Week
13280
Placebo
Combined

Table 1: Organs Evaluated in the Physician Organ Assessment Score (POST)*

- Lungs
- Skin
- Peripheral Lymph Nodes
- Eyes
- Liver
- Spleen
- Neurologic CNS
- Neurologic Peripheral
- Parotid/Salivary Glands
- Bone marrow
- Ear
- Nose
- Throat
- Cardiac
- Renal
- Bone/Joint
- Muscle
- Gastrointestinal

* extrapulmonary Physician Organ Severity Tool (ePOST) includes all organs except the lungs.

Table 2: Severity Assessment of Each Organ

Score	Description
0	Not affected
1	Slight
2	Mild
3	Moderate
4	Moderate to severe
5	Severe
6	Very severe

Table 3: Patient Baseline Characteristics

Characteristic	Placebo (n=45)	Combined Infliximab (n=93)	Total (n=138)
Age*	45.3 ± 9.4	47.8 ± 9.1	47.0 ± 9.3
Male †	26 (57.8)	52 (55.9)	78 (56.5)
Race †			
- Caucasian	29 (64.4)	64 (68.8)	93 (67.4)
- Black	16 (35.6)	25 (26.9)	41 (29.7)
- Asian	0 (0.0)	2 (2.2)	2 (1.4)
- Other	0 (0.0)	2 (2.2)	2 (1.4)
Extrapulmonary involvement ‡	30/45 (66.7)	62/91 (68.1)	92/136 (67.6)
Years since histologically proven sarcoidosis*	7.0 ± 6.2	6.9 ± 6.2	0.9 ± 6.2††
Forced vital capacity (Liters)*	2.86 ± 0.77	2.82 ± 0.78	2.83 ± 0.78
Forced vital capacity (Percent of predicted)*	68.8 ± 11.1	68.6 ± 9.1	68.7 ± 9.7

* Mean ± SD
† n **(%)**
‡ n/total (%)
†† n=137

Table 4. Frequency of Extrapulmonary Organ Involvement at Baseline, N=136*

	Patients Affected	
Organ	**N**	**Percent†**
Lungs	136	100%
Peripheral Lymph Nodes	50	37%
Skin	36	26%
Bone/Joint	27	20%
Liver	19	14%
Eyes	19	14%
Muscle	18	13%
Cardiac	12	9%
Peripheral Nervous System	11	8%
Nose	11	8%
Central Nervous System	9	7%
Spleen	8	6%
Renal	8	6%
Bone Marrow	5	4%
Throat	3	2%
Parotid/Salivary Glands	3	2%
Ear	1	1%
Gastrointestinal	1	1%

* Two patients were randomized but did receive study agent; thus, ePOST assessments were not performed.

† Percentages have been rounded.

Table 5: Change in Number of Extrapulmonary Organs Involved from Baseline to Week 24

Change in Organ number	Placebo N=44	Combined Infliximab N=89
≤ -1	7 (16%)	34 (38%)
0	30 (68%)	49 (55%)
≥ 1	7 (16%)	6 (7%)

Table 6. Mean change in sarcoidosis organ score for each organ

Organ	Placebo, N = 44						Combined Infliximab, N = 89						Wilcoxon p value (t approx.)
	Mean	±	SD	[Min,Max]	# of pt at Base*	# of pt at W24†	Mean	±	SD	[Min,Max]	# of pt at Base*	# of pt at W24†	
Bone/Joint	-0.1	±	0.85	[-2, 4]	8	8	-0.2	±	0.57	[-3, 1]	19	11	0.580
Bone Marrow	0.0	±	0.46	[-2, 2]	3	3	0.0	±	0.24	[-1, 2]	2	3	0.524
Cardiac	0.0	±	0.30	[0, 2]	4	4	-0.1	±	0.36	[-2, 1]	8	4	0.111
Central nervous system	0.1	±	0.78	[-1, 4]	3	5	0.0	±	0.15	[-1, 0]	6	5	0.582
Eyes	0.0	±	0.46	[-1, 2]	7	9	-0.1	±	0.61	[-3, 2]	12	10	0.841
Liver	0.0	±	0.30	[-1, 1]	3	3	-0.2	±	0.54	[-3, 1]	15	8	0.096
Lymph Nodes	-0.4	±	0.79	[-3, 0]	19	14	-0.3	±	0.75	[-3, 2]	31	23	0.390
Muscle	-0.1	±	0.47	[-2, 1]	7	6	-0.1	±	0.44	[-2, 1]	11	9	0.588
Nose	0.1	±	0.59	[-2, 3]	3	4	-0.1	±	0.63	[-4, 1]	7	6	0.236
Peripheral nervous system	0.0	±	0.51	[-3, 1]	4	4	-0.1	±	0.38	[-2, 1]	7	6	0.281
Renal	0.0	±	0.15	[0, 1]	1	2	0.0	±	0.32	[-1, 2]	7	5	0.293
Skin	-0.1	±	0.69	[-4, 1]	8	8	-0.3	±	0.90	[-5, 2]	26	17	0.087
Spleen	0.0	±	0.15	[0, 1]	0	1	-0.1	±	0.38	[-2, 0]	8	5	0.061

* number of patients with involvement of that organ (organ score ≥1) at baseline
† number of patients with involvement of that organ (organ score ≥1) at week 24

Table 7: Change in ePOST of Minor and Major Organs between Week 0 and Week 24.

	Placebo (N = 44)						Combined Infliximab (N = 89)						Willcoxon Rank Sum test with t approximation p-value
	Baseline		Week 24		Change		Baseline		Week 24		Change		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
ePOST(minor)	2.50	3.91	1.91	3.17	-0.59	2.19	2.28	2.96	1.29	2.00	-0.99	1.96	0.174
ePOST(major)	1.41	2.73	1.52	2.67	0.11	1.24	1.12	1.85	0.74	1.34	-0.38	1.13	0.178

Notes:

(1) ePOST(minor) is the sum of the scores for bone/joint, lymph nodes, muscle, nose, skin, and spleen.

(2) ePOST(major) if the sum of the scores for bone marrow, cardiac, CNS, liver, PNS, renal, and eyes.

(3) Other organs including ear, parotid/salivary glands, GI, and throat are not included in this analysis because the number of subjects with involvement is too small.

(4) This analysis only includes subjects with data available at both baseline and week 24.

Appendix 1 – Centocor T48 Sarcoidosis Investigators

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