SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 289-295

Infliximab for chronic cutaneous sarcoidosis: a subset analysis from a double-blind randomized clinical trial

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Abstract. *Background:* Limited evidence exists demonstrating an effective treatment for chronic cutaneous sarcoidosis. *Objective:* To determine infliximab's effectiveness in sarcoidosis. *Methods:* We conducted a subset analysis from a randomized, double-blind, placebo-controlled trial for chronic pulmonary sarcoidosis to determine infliximab's effectiveness. Patients with chronic cutaneous sarcoidosis received infliximab (3 or 5 mg/kg) or placebo over 24 weeks. Of 138 patients, the subset analysis evaluated 17 patients with chronic facial and another 9 patients with nonfacial skin involvement. The SASI evaluated lesions for degree of erythema, desquamation, induration, and percentage of area involved. Facial and nonfacial lesions were scored in a blinded manner. *Results:* Among 5 placebo-treated and 12 infliximab-treated patients, an improvement was observed with infliximab versus placebo in change from baseline to weeks 12 and 24 in desquamation (P<0.005) and induration (P<0.01) at week 24. Erythema, percentage of area involved and the evaluation of paired photographs did not reveal significant differences. *Limitations:* Sample size; more extensive disease in placebo patients; chronic therapy upon enrollment; lung as primary organ of sarcoidosis involvement; limited investigator experience with SASI. *Conclusions:* Infliximab appears to be a beneficial treatment for chronic cutaneous sarcoidosis. The SASI scoring system demonstrated significant improvement versus placebo in lesion desquamation and induration. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 289-295)*

Key words: infliximab; cutaneous sarcoidosis; pulmonary; sarcoidosis; sarcoidosis activity and severity index; tumor necrosis factor-alpha

Acronyms and abbreviations

FVC, forced vital capacity
LuPGA, lupus pernio physician global assessment
MCS, score and mental component summary
PCS, physical component summary
QOL, quality of life
SASI, Sarcoidosis Activity and Severity Index
SF-36, Short Form-36 Health Survey Questionnaire
TNF-α, tumor necrosis factor-alpha

Received: 2 October 2014
Accepted after revision: 3 August 2015
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Trial Registration: http://www.clinicaltrials.gov; NCT00073437

Introduction

Infliximab is a chimeric monoclonal antibody that binds to tumor necrosis factor-alpha (TNF-α). The first published series demonstrating effectiveness

of infliximab for sarcoidosis included 2 patients with refractory lupus pernio who demonstrated a response to infliximab (1). Others have found infliximab beneficial for the treatment of refractory chronic cutaneous sarcoidosis (2-6). A retrospective analysis of 54 sarcoidosis patients with lupus pernio found that treatment regimens including infliximab were more likely to result in skin lesion improvement compared with other regimens (7).

We previously reported that infliximab was beneficial for the treatment of chronic pulmonary sarcoidosis (8). Patients with pulmonary disease and lupus pernio underwent serial skin lesion evaluations by the local investigator administering the lupus pernio physician global assessment (LuPGA). Although no significant differences were noted in the scores between those treated with placebo or infliximab, there was a tendency for infliximab-treated patients to demonstrate a reduced LuPGA score (8).

We have reported on the validity and reproducibility of 2 different scoring instruments for chronic cutaneous facial sarcoidosis. The first scoring instrument, the Sarcoidosis Activity and Severity Index (SASI), evaluates individual facial lesions for erythema, induration, desquamation, and percent of total area involved (9). The SASI also identifies specific attributes of an individual skin lesion which could change with therapy (10). The second scoring instrument, the comparison of photographs of lesions pre- and post-treatment, has also been used to assess response to therapy (7, 10, 1).

We report the effectiveness of infliximab in the treatment of chronic cutaneous sarcoidosis, based on the results of the SASI and the evaluation of pre- and post- treatment photographs, of patients who participated in the previously published double-blind randomized trial of infliximab for chronic pulmonary sarcoidosis (8). We aimed to determine if either of these evaluations would demonstrate a significant improvement in the cutaneous sarcoidosis of patients receiving infliximab treatment versus placebo (8).

Methods

A detailed description of the original study design and main clinical outcomes has been previously published (8). In brief, this was a multicenter study conducted between September 30, 2003, to August 31, 2004, consisting of 34 sites from 15 countries in the US and Europe. All patients were diagnosed with chronic pulmonary sarcoidosis based on standard criteria (12), and all patients underwent a biopsy of ≥1 site demonstrating noncaseating granulomas, a clinical presentation consistent with sarcoidosis. All patients were aged ≥18 years and received a sarcoidosis diagnosis ≥1 year prior to enrollment. Additional entry criteria included parenchymal lung disease by chest roentgenogram, a forced vital capacity (FVC) of 50-85% of predicted FVC, and persistent dyspnea despite therapy. The primary endpoint was improvement in FVC after 24 weeks of infliximab treatment. Patients with skin or eye involvement were also encouraged to participate as part of a secondary objective to determine the efficacy of infliximab in the treatment of extrapulmonary manifestations of chronic sarcoidosis, particularly the skin and eyes. Prior to study enrollment, all patients received ≥10 mg daily of prednisone or its equivalent and/or methotrexate, azathioprine, or hydroxychloroquine for ≥3 months prior to randomization. The dose of these agents was required to remain stable and consistent for ≥3 months prior to study entry. After providing written informed consent, patients were randomized to receive either placebo or 3 or 5 mg/kg of intravenous infliximab at weeks 0, 2, 6, 12, 18, and 24. The protocol was approved by each institution's ethics committee or institutional review board.

In this subset analysis of patients with chronic cutaneous sarcoidosis, patients with facial skin lesions were evaluated using the SASI. Evaluations were conducted using a standardized scoring sheet which divided the face into 4 quadrants. The face was divided into superior and inferior sections by a horizontal line through the middle of the eyes, with the ears located in the inferior section, and divided laterally by a vertical line through the middle of the nose. A facial lesion in the upper left quadrant of a study patient's face, before and after 18 weeks of 3 mg/kg infliximab therapy, is shown in eFigure1. The degree of erythema, desquamation, and induration was reported for each quadrant using a Likert scale from 0-4 (0=none, 4=very severe). The percentage of total area involved for each quadrant was scored from 0-6 (0=no involvement, 6=90-100% involvement). This scoring system was similar to one that we previously reported (9), except that currently, the nose is included and scored as 1 of the 4 quadrants and not as a

separate area unto itself. Each patient was evaluated and scored by the same investigator prior to treatment and subsequently at each study visit. At study initiation, a training session on SASI was provided. Examples of skin lesions were presented, including cards that demonstrated the amount of erythema and induration for each score on the Likert scale, and the scoring system was discussed to ensure consistent inter- and intra-investigator scoring.

Photographs of patients' most involved skin lesions on the face, arms, or legs were taken at the initial visit. The photographs were compared with week-24 photographs of the same lesions (or week-18 photographs when week-24 photographs were unavailable) after the conclusion of the trial. Photographs were presented to readers in a blinded fashion for treatment and visit order. Three readers (RPB, MAJ, EEL) evaluated the photographs and scored the lesions. A score of "better" at week 24 compared with the initial visit was assigned 2 points, and a score of "somewhat better" was assigned 1 point. A score of "better" at the initial visit compared with week 24 was assigned -2 points and "somewhat better" was assigned -1 point. "No difference" between the initial visit and week 24 was assigned 0 points. Scores for each patient were averaged and reported by treatment group. A lesion scored as "better," after 18 weeks of 3-mg/kg infliximab therapy, by all 3 readers is shown in eFigure 1.

The Short Form-36 Health Survey Questionnaire (SF-36) (13) was administered to all patients at weeks 0, 12, and 24. The change in the SF-36 physical component summary (PCS) score and mental component summary (MCS) score from baseline to weeks 12 and 24 were used to measure quality of life (QOL) in infliximab-treated patients versus placebo-treated patients.

Statistical analysis

SASI scores were summarized using median and range. To analyze the data, comparisons were performed between placebo-treated patients and infliximab-treated patients who received either 3 or 5 mg/kg. Individual quadrants were considered experimental units in the analyses. Separate comparisons were performed for each SASI feature. Due to the skewness of the scores, nonparametric analysis using the Mann-Whitney U test was performed. As a result of the post hoc nature of the analyses, all *P* values were considered nominal.

Results

Seventeen of the 138 patients from the original clinical study with chronic cutaneous sarcoidosis involving the face were evaluated. This included 5 patients who received placebo, 4 patients who received 3 mg/kg infliximab, and 8 patients who received 5 mg/kg infliximab. Figure 1 displays the Consolidated Standards of Reporting Trials (14) flowchart summarizing patient participation in this study. Patients received scheduled treatments and were evaluated at weeks 12 and 24.

Although the lung is the most common organ involved, the skin can frequently be affected. Cutaneous skin lesions can be classified as specific or non-specific, with specific skin lesions being those that tend to be more chronic, difficult to treat, and are associated with worse outcomes (15). In this particular study, investigators were encouraged to enroll subjects who presented with chronic cutaneous facial lesions. These lesions are often commonly referred to as lupus pernio. Lupus pernio is the term used for the collective presentation of distinctive, symmetric, violaceous, indurated plaquelike and nodular fibrotic lesions that occur primarily on the face, ears, and digits (16).

Due to the small number of patients with chronic facial disease in this study, the placebo-treated patients were compared with the combined infliximab-treated patients (ie, patients who received either 3 or 5 mg/kg of infliximab). Table 1 illustrates the baseline demographics and disease characteristics of the 17 patients analyzed in the chronic facial substudy. In general, the placebo- and infliximab-treated groups were similar.

Table 1 also shows the distribution of chronic facial lesions across all facial quadrants (4 quadrants per patient) for the SASI evaluation for both placebo- and infliximab-treated patients. Each quadrant was analyzed for the presence of erythema, induration, or desquamation. At baseline, patients assigned to placebo appeared to have slightly more extensive cutaneous sarcoidosis with 15/20 quadrants (75.0%) demonstrating chronic facial involvement versus 26/48 quadrants (54.2%) in the infliximab group.

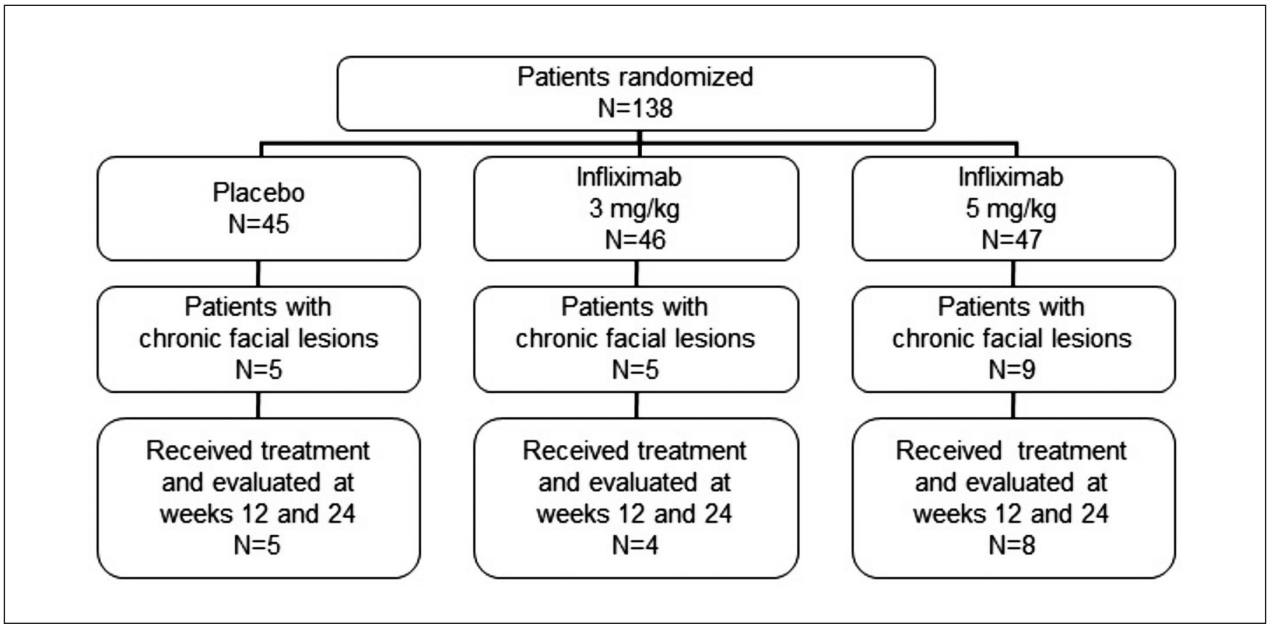

Fig. 1. Flow diagram of sarcoidosis patients who participated in the original study and in the chronic facial subgroup

Table 1. Baseline demographics and disease characteristics

	Placebo	Infliximab
Patients, n	5	12
Age†	40 (36, 53)	47 (34, 56)
Male:Female	2:3	5:7
Black:White:Other	4:1:0	6:5:1
Baseline FVC % predicted‡	71.0±12.17	67.4±9.25
Baseline SF-36‡		
PCS	36.5±12.66	29.7±7.89
MCS	45.2±7.19	49.3±13.02
Skin features: per quadrant		
Total number of quadrants	20	48
Any involvement	15 (75.0%)	26 (54.2%)
Erythema	14 (70.0%)	19 (39.6%)
Induration	14 (70.0%)	21 (43.8%)
Desquamation	10 (50.0%)	12 (25.0%)

FVC, forced vital capacity; *SF-36*, short form-36 health survey questionnaire; *PCS*, physical component summary score; *MCS*, mental component summary score.
†Median (Range)
‡Mean±SD

The occurrence of erythema, induration, and desquamation were all greater in placebo-treated patients than in infliximab-treated patients; however, erythema and induration were more frequently observed compared with desquamation irrespective of treatment group.

Table 2 compares the median (range) change in SASI score from baseline to week 12 and 24, for erythema, induration, desquamation, and percentage of area involved. Infliximab-treated patients demonstrated a significant reduction in the score for induration at week 24 (P=0.009) and a significant reduction in desquamation at week 12 (P=0.004) and 24 (P=0.004); however, there was no significant difference between the placebo group and the infliximab group for the change in erythema score or percentage of total facial area involved at either week 12 or 24.

Figure 2 shows the change from baseline in the desquamation score for both the placebo and infliximab groups at week 24, whereby only 1/10 quadrants (10.0%) in the placebo group showed a reduction. Eleven of 12 quadrants (91.7%) in the infliximab group, however, showed a reduction in desquamation, including a 2-point decrease in 4 quadrants (33.3%). Figure 3 shows the change from baseline in the induration score for both treatment groups at week 24. A greater number of quadrants in the infliximab group demonstrated a reduction in induration. Thirteen of 21 quadrants (61.9%) demonstrated a reduction, including 6/21 quadrants (28.6%) demonstrating a ≥2-point decrease. In contrast, only 3/14 quadrants (21.4%) demonstrated a reduction in induration score in the placebo group and no quadrants experienced a ≥2-point change in score.

The analysis based on the target quadrants is shown in eTable 1. Due to the small sample sizes of both treatment groups, the changes for erythema,

Table 2. Comparison of changes in SASI during treatment

SASI feature	Number of quadrants affected at baseline		Change in SASI score from baseline									
			Week 12					Week 24				
			Placebo (n=5)		Infliximab (n=12)		*P* value	Placebo (n=5)		Infliximab (n=12)		*P* value
	Placebo	Infliximab	median	range	median	range		median	range	median	range	
Erythema	14	19	0	(-2,0)	0	(-2,1)	0.37	-1	(-2,0)	0	(-2,1)	0.11
Induration	14	21	0	(-2,0)	-1	(-3,1)	0.24	0	(-1,1)	-1	(-3,0)	0.009
Desquamation	10	12	0	(-1,1)	-1.5	(-2,0)	0.004	0	(-2,0)	-1	(-2,0)	0.004
Area	15	26	0	(-1,0)	-0.5	(-4,0)	0.21	0	(-2,0)	-1	(-4,0)	0.13

SASI, sarcoidosis activity and severity index

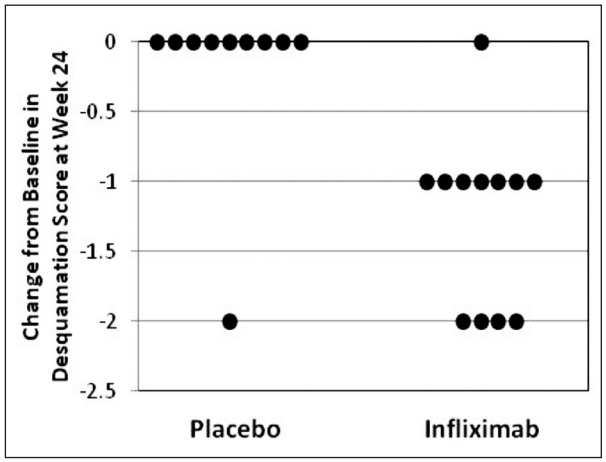

Fig. 2. Placebo-treated patients compared with infliximab-treated patients for the change in desquamation from baseline to week 24 for the SASI evaluation. *P*=0.004

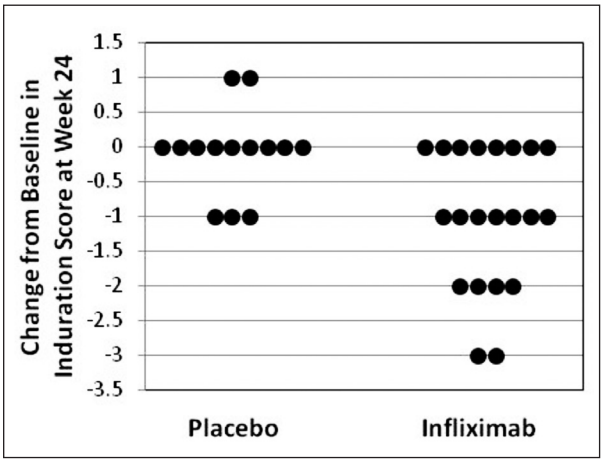

Fig. 3. Placebo-treated patients compared with infliximab-treated patients for the change in induration from baseline to week 24 for the SASI evaluation. *P*=0.009

induration, desquamation, and area involved were all nonsignificant.

Five of the 12 (41.7%) infliximab-treated patients were SASI responders, including 4 marked SASI responders, compared with 0/5 (0.0%) placebo-treated patients. No significant difference was observed between treatment groups, although the proportion of SASI responders was greater in the 5-mg/kg infliximab group than in the 3-mg/kg infliximab group (50.0% versus 25.0%, respectively). An additional 2 infliximab-treated patients were partial SASI responders compared with 1 placebo-treated partial SASI responder.

Initial and follow-up photographs of 23 skin lesions were read in a blinded manner by 3 investigators. Fourteen of the skin lesions were facial lesions from the 17 patients with chronic facial lesions who had been evaluated with SASI (the remaining 3 patients did not have paired photographs that were adequate for analysis), and 9 of the evaluated skin lesions were nonfacial lesions from additional original study patients with skin involvement. Agreement was generally good with only 3 of 23 readings deviating by >1 category for all 3 readers. The average of the 3 investigators' scores for each set of paired photographs is shown in Figure 4. No significant differences were observed between the combined infliximab group and placebo group nor between the 3 different treatment groups, although the mean and median scores of the photographic analysis for the 5-mg/kg infliximab group were numerically higher (0.70 and 1.00, respectively) than the 3-mg/kg infliximab group (0.06 and 0.00) and the placebo group (-0.04 and -0.67). The mean and median scores for the combined infliximab group, for just the 14 patients with cutaneous facial sarcoidosis, were also numerically higher (0.17 and -0.17) than the placebo group (-0.06 and -0.67).

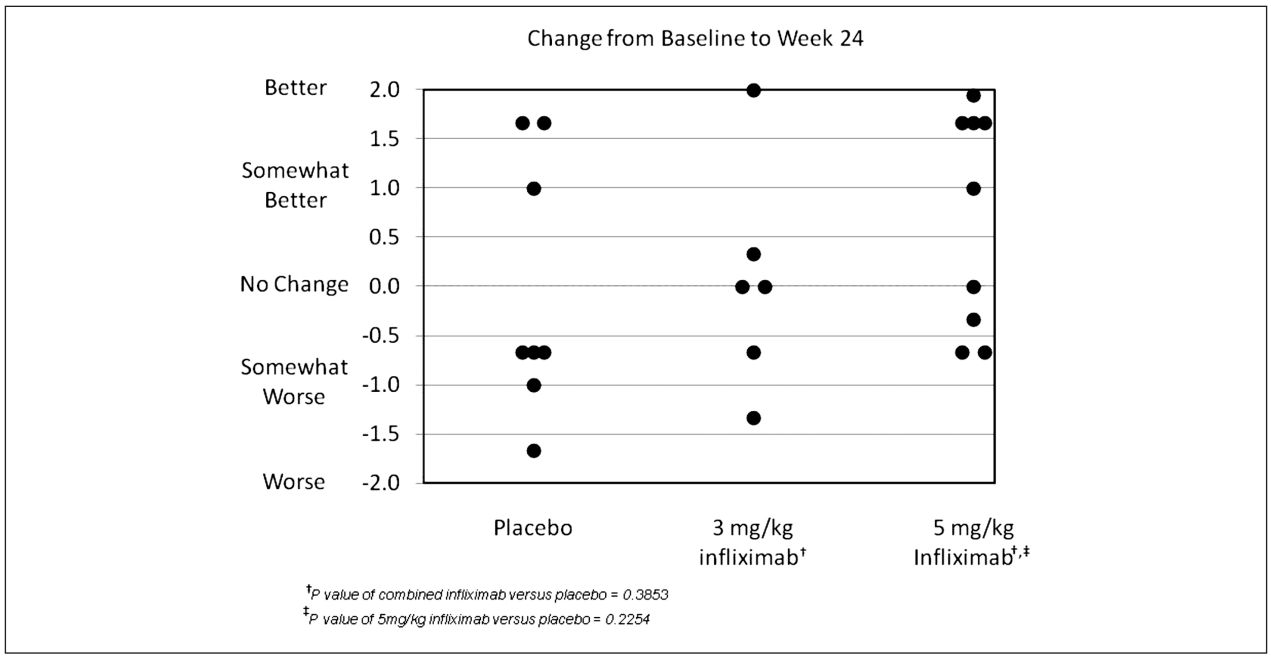

Fig. 4. Change in the photographic comparison from baseline to week 24 for the 3 different treatment groups (placebo, 3 mg/kg infliximab, 5 mg/kg infliximab)

Due to the small sample sizes of both treatment groups, significant differences between the groups were not determined; however, the mean±SD change from baseline to week 24 for the SF-36 PCS and MCS scores were numerically higher for the combined infliximab group (3.6±8.87 and -0.6±7.42, respectively) compared with the placebo group (-2.1±6.83 and -3.8±5.62, respectively).

Discussion

We found that infliximab appeared to be more effective than placebo for the treatment of immunosuppressant therapy-resistant chronic cutaneous sarcoidosis. The SASI instrument captured significant differences in changes in facial lesions between patients treated with infliximab and patients treated with placebo. The most significant changes were identified as reductions in desquamation and induration in patients treated with infliximab; however, there was no documented significant difference in erythema or total facial area involved with infliximab versus placebo treatment. The proportion of infliximab-treated SASI responders compared with placebo-treated SASI responders suggests an advantage to the 5-mg/kg dose of infliximab in the treatment of chronic cutaneous sarcoidosis. While the comparison of pre- and post-treatment photographs did not demonstrate any statistically significant differences between treatment groups, the mean and median scores also suggest a possible benefit of infliximab compared with placebo, particularly at the 5-mg/kg dose. Additionally, the greater changes from baseline SF-36 PCS and MCS scores for the infliximab group versus the placebo group suggest a possible improvement in QOL with infliximab in this subset of chronic cutaneous sarcoidosis patients; however, the small number of patients prevented statistical confirmation.

Using a previously validated skin lesion assessment instrument (9), the current study was able to demonstrate a significant improvement in patients with chronic facial lesions treated with infliximab compared with placebo over 24 weeks. In the validation trial, good to excellent intraobserver reproducibility was reported for all 4 features of the SASI. On repeated evaluation of a stable skin lesion, the SASI score varied by ≤1 point in over 95% of cases evaluated. Therefore, changes of ≥2 points due to chance

were considered unlikely (9). As noted in Figures 2 and 3, in the placebo group, only 1/24 SASI scores for desquamation and induration differed by ≥2 points from baseline while, in the infliximab group, 10/33 SASI scores decreased by ≥2 points.

In contrast to the comparison of pre- and post-treatment photographs, the SASI demonstrated significant improvement of facial lesions in patients treated with infliximab. Significant improvement, however, was only noted with the desquamation and induration scores. We were unable to demonstrate a change for the index quadrants for either desquamation or induration. This may have been due to the small number of patients in each group and the fact that placebo-treated patients appeared to have slightly more extensive cutaneous sarcoidosis at baseline. Also, all patients were on stable, chronic therapy, which may have tempered any response to additional therapy. Furthermore, patients enrolled in the study were required to have the lung as the primary organ of sarcoidosis involvement. The results support the value of the SASI system in monitoring response to therapy in chronic cutaneous sarcoidosis. The inability to demonstrate significant changes in skin lesions using paired photographic analysis may reflect small study patient numbers. In addition, 2-dimensional photographic examination cannot evaluate induration. For multicenter trials, standardization of photographic conditions can minimize but not eliminate the inherent variability of serial photographs (17).

In summary, infliximab was an effective treatment of chronic cutaneous sarcoidosis. In an area with little evidence supporting a specific treatment agent, [18] this study demonstrated significant improvement in features of facial lesions in a subset analysis of a prospective, blinded, randomized, placebo-controlled multinational trial in sarcoidosis.

Funding Source/Conflicts of Interest

This study was supported by Janssen Research & Development, LLC, a subsidiary of Johnson & Johnson. The sponsor contributed to the design and conduct of the study; the collection, analysis, and interpretation of data; and the preparation, review, or approval of the manuscript.

Baughman, Judson, Lower, Costabel, and Drent have received research grants from Janssen Research and Development, LLC. Flavin, Lo, and Barnathan are employed by Janssen Research and Development, LLC, and own stock in Johnson & Johnson.

References

1. Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG/World Association of Sarcoidosis and Other Granulomatous Disorders 2001; 18 (1): 70-4.
2. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. Chest 2005; 127(3): 1064-71.
3. Heffernan MP, Anadkat MJ. Recalcitrant cutaneous sarcoidosis responding to infliximab. Archives of dermatology 2005; 141(7): 910-1.
4. Mallbris L, Ljungberg A, Hedblad MA, Larsson P, Stahle-Backdahl M. Progressive cutaneous sarcoidosis responding to anti-tumor necrosis factor-alpha therapy. Journal of the American Academy of Dermatology 2003; 48(2): 290-3.
5. Saleh S, Ghodsian S, Yakimova V, Henderson J, Sharma OP. Effectiveness of infliximab in treating selected patients with sarcoidosis. Respiratory medicine 2006; 100(11): 2053-9.
6. Sweiss NJ, Welsch MJ, Curran JJ, Ellman MH. Tumor necrosis factor inhibition as a novel treatment for refractory sarcoidosis. Arthritis and rheumatism 2005; 53(5): 788-91.
7. Stagaki E, Mountford WK, Lackland DT, Judson MA. The treatment of lupus pernio: results of 116 treatment courses in 54 patients. Chest 2009; 135(2): 468-76.
8. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du Bois R, Albera C, Brutsche M, Davis G, Donohue JF, Muller-Quernheim J, Schlenker-Herceg R, Flavin S, Lo KH, Oemar B, Barnathan ES, Sarcoidosis I. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. American journal of respiratory and critical care medicine 2006; 174(7): 795-802.
9. Baughman RP, Judson MA, Teirstein A, Lower EE, Lo K, Schlenker-Herceg R, Barnathan ES. Chronic facial sarcoidosis including lupus pernio: clinical description and proposed scoring systems. American journal of clinical dermatology 2008: 9(3): 155-61.
10. Baughman RP, Judson MA, Ingledue R, Craft NL, Lower EE. Efficacy and safety of apremilast in chronic cutaneous sarcoidosis. Archives of dermatology 2012; 148(2): 262-4.
11. Baughman RP, Judson MA, Teirstein AS, Moller DR, Lower EE. Thalidomide for chronic sarcoidosis. Chest 2002; 122(1): 227-32.
12. Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, Eklund A, Kitaichi M, Lynch J, Rizzato G, Rose C, Selroos O, Semenzato G, Sharma OP. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG/World Association of Sarcoidosis and Other Granulomatous Disorders 1999; 16(2): 149-73.
13. Ware JE, Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Medical care 1992; 30(6): 473-83.
14. Moher D, Schulz KF, Altman DG, Consort G. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. Annals of internal medicine 2001; 134(8): 657-62.
15. Mana J, Marcoval J, Graells J, Salazar A, Peyri J, Pujol R. Cutaneous involvement in sarcoidosis. Relationship to systemic disease. Archives of dermatology 1997; 133(7): 882-8.
16. Marchell RM, Judson MA. Chronic cutaneous lesions of sarcoidosis. Clinics in Dermatology 2007; 25(3): 295-302.
17. Bae Y, Nelson JS, Jung B. Multimodal facial color imaging modality for objective analysis of skin lesions. Journal of biomedical optics 2008; 13(6): 064007.
18. Baughman RP, Lower EE. Evidence-based therapy for cutaneous sarcoidosis. Clin Dermatol 2007; 25(3): 334-40.