Beneficial effect of infliximab on refractory sarcoidosis

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ABSTRACT

INTRODUCTION: Sarcoidosis is a systemic granulomatous disease. Evidence suggests that tumour necrosis factor-alpha (TNF-α) is important in the pathophysiology, and TNF-α-inhibitors such as infliximab are therefore used against sarcoidosis refractory to traditional therapies or where side effects to these are intolerable. The aim of this retrospective study was to investigate the effect of infliximab on refractory sarcoidosis.

MATERIAL AND METHODS: Twelve patients were treated with infliximab and their medical records were reviewed. Efficiency was evaluated based on changes in P-angiotensin-converting enzyme (P-ACE) and P-interleukin-2 (P-IL-2), pulmonary function tests and chest radiographs (stage I-IV) after seven treatments and at the end of treatment. The effect of infliximab on extrapulmonary sarcoidosis was described separately for ocular and cutaneous sarcoidosis.

RESULTS: Patients with pulmonary symptoms (n = 9) obtained an average increase in forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), total lung capacity (TLC) and diffusion capacity for carbon monoxide (T_LCO) after treatment with infliximab. One patient with radiographic stage I at baseline obtained a normal radiograph after treatment. Changes in radiographic staging were observed for no other patients. The mean value of both P-ACE and P-IL-2 in patients with raised values pre-treatment (n = 6) decreased to values with-in the reference interval after treatment. Furthermore, infliximab had a steroid sparing effect on ocular sarcoidosis (n = 2) and an effect on cutaneous sarcoidosis (n = 2) based on clinical evaluations.

CONCLUSION: Our results suggest that infliximab is an effective treatment against refractory pulmonary and extrapulmonary sarcoidosis. Other studies have shown similar results.

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Sarcoidosis is a multisystem granulomatous disease with an incidence in Denmark of 7.2 per 100,000 person years. The disease affects the lungs and the mediastinal lymph nodes in more than 90% of cases. The aetiology remains unknown, but the nature of the immune response and a tendency to familiar accumulation suggest that the disease arises in genetically suscep-tible individuals who have been exposed to a certain kind of agent. The most likely theory is that the agent is of infectious origin [1].

The primary treatment is corticosteroids, but in the case of unacceptable side effects or lack of response, treatment is often supplemented with other immunosuppressants such as methotrexate (MTX), azathioprin, mofetil mycophenolat or tumour necrosis factor-alpha (TNF-α)-inhibitors such as infliximab. Infliximab is a chimeric, monoclonal antibody directed against TNF-α which consists of a human constant part and a murin variable part. The formation of the non-caseating granuloma seen in sarcoidosis is caused by an inflammatory response mediated by cytokines released from activated immunocells. TNF-α is one of the most important cytokines, and it is therefore believed that infliximab can be used against sarcoidosis. Infliximab binds both soluble and cell-bound TNF-α thereby inhibiting the function of the cytokine. Fur-thermore, it has been shown that infliximab also binds to peripheral lymphocytes and induces apoptosis when these cells are activated [2, 3].

Several case series describe an effect of infliximab on sarcoidosis, but only two randomized trials have so far been performed [2, 4]. Both studies showed an increase in the lung function of patients treated with infliximab compared with the placebo group, but the increase was only significant ($p < 0.05$) in the study by Baughman et al [4].

In Denmark, infliximab is used against sarcoidosis refractory to standard immunotherapy or in cases where side effects of standard therapy are intolerable. The aim of this retrospective study was to evaluate the effect of infliximab in patients with sarcoidosis treated at the Department of Respiratory Medicine and Allergology, Aarhus University Hospital.

MATERIAL AND METHODS

From August 2005 to November 2010, twelve patients (seven males and five females) with sarcoidosis were treated with infliximab. Their medical records were re-

ABBREVIATIONS

FEV1 = forced expiratory volume in the first second
FVC = forced vital capacity
P-ACE = P-angiotensin-converting enzyme
P-IL-2 = P-interleukin-2
TLC = total lung capacity
T_LCO = diffusion capacity for carbon monoxide
TNF-α = tumour necrosis factor-alpha

ORIGINAL ARTICLE

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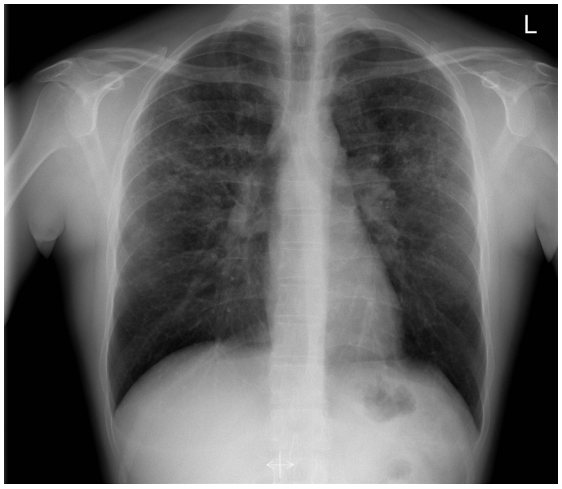


Patient with sarcoidosis stadium II.

viewed to retrieve rele-vant information. Before treatment with infliximab was initiated, a diagnosis was secured in the usual way which included bioptic verification. One patient was diagnosed without biopsy because she presented with Löfgren's syndrome (chronic uveitis, erythema nodosum and hilar lymphadenopathy). All patients were tested with T-spot, and screening for hepatitis B and C were carried out in order to rule out latent tuberculosis and hepatitis.All patients were monitored with pulmonary function tests (forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), total lung capacity (TLC) and diffusion capacity for carbon monoxide (T_LCO) (ZAN 530 BodySystem (Inspire-health) and Jaeger MasterScreen PFT probody (VI-ASYS Healthcare)), radiographs (stage I-IV) and blood samples (P-angiotensin-converting en-zyme (P-ACE) and P-interleukin-2 (P-IL-2)).

The effect of infliximab on extrapulmonary sarcoidosis was evaluated separately based on clinical observation and specific examinations. Patient-experienced improvements and occurrence of side effects were also noted.

Trial registration: not relevant.

RESULTS

The population

The baseline characteristics of the population are presented in **Table 1**. The mean age at time of diagnosis was 34 years (22-51 years). All patients had lung involvement based on radio-graphs, but three of the patients were without pulmonary symptoms and with normal pulmo-nary function. Except from pulmonary sarcoidosis, the patients had symptoms from the eyes (n = 2), skin (n = 2), oesophagus (n = 1), bone marrow (n = 1), kidney (n = 1), lymph nodes (n = 1) and nose (n = 1) when infliximab treatment was initiated. Only organs affected in two or more patients will be described in detail.

Infliximab was initiated because of intolerable side effects (n = 2), lack of response to stand-ard immunotherapy (n = 2), or a combination of both (n = 8). The initial dosage was 3 mg/kg in all patients except one with ocular sarcoidosis who started on 5 mg/kg. In two other pa-tients (one with ocular and one with pulmonary sarcoidosis), the dosage was increased to 5 mg/kg during the treatment course. Treatment was given at week 0, 2 and 6. If more than four months between two infusions with infliximab occurred, it was considered as if the patient had initiated a new treatment course (n = 2). For most patients, treatment was administered at eight-week intervals. If there was more than four months between two treatments, the treatments were considered as two separate treatment courses (n = 2). The mean duration of infliximab treatment was 25 months (3–56)

TABLE 1

Baseline characteristics of the twelve patients.

Gender, n (%)	
Male	7 (58)
Female	5 (42)
Race, n (%)	
Caucasian	11 (92)
Black	1 (8)
Age at the time of diagnosis, years, mean (range)	34 (22-51)
Radiographic stage at baseline, n (%)	
Stage I: BHL	3 (25)
Stage II: BHL and PI	4 (33)
Stage III: PI	3 (25)
Stage IV: PF	2 (17)
Time from diagnosis to initiation with infliximab, months, mean (range)	70 (8-228)
Organ involvement, n (%)	
Pulmonary sarcoidosis	9 (75)
Cutaneous sarcoidosis	2 (17)
Ocular sarcoidosis	2 (17)
Oesophagus sarcoidosis	1 (8)
Bone marrow sarcoidosis	1 (8)
Renal sarcoidosis	1 (8)
Lymph node sarcoidosis	1 (8)
Nose sarcoidosis	1 (8)
Treatment before infliximab, n (%)	
Prednisolon	12 (100)
Methotrexate	11 (92)
Azathioprin	6 (50)
Peribulbar glucocorticoid injection	2 (17)
Cyclosporine	1 (8)
Treatment with infliximab, mean (range)[a]	
Duration, months	25 (3-56)
Treatments, n	15 (4-27)

BHL = Bilateral hilar lymphadenopathy; PF = pulmonary fibrosis; PI = pulmonary infiltrates.
a) Six of the patients are still receiving infliximab treatment.

and the mean number of treatments was 15 (4–27). Six patients were still being treated with infliximab at the time of this survey (Table 1).

During treatment with infliximab, patients were also treated with other immunosuppressants in order to achieve both a synergetic effect and, more importantly, to prevent the immune system from developing antibodies to infliximab.

Pulmonary sarcoidosis

All patients had pulmonary changes on their chest radiographs (Table 1). After treatment with infliximab, the radiograph normalized in one patient with extrapulmonary sarcoidosis (stage I before infliximab). Staging changed in none of the other patients' radiograms.

The effect of infliximab on pulmonary sarcoidosis was evaluated by changes in the lung func-tion parameters (FEV1, FVC, TLC and T_LCO). The measurements were collected just before infliximab therapy was initiated, after seven treatments and after the last dosage was given. The mean change was calculated for two groups: group A included all patients (n = 12) and also patients with two treatment courses (n = 2), and group B included only patients with pulmonary symptoms (n = 9). After seven treatments, a mean increase in FEV1, FVC and TLC was seen in both groups. T_LCO unexpectedly decreased compared with the baseline value. After the last treatment, there was a mean increase in all pulmonary parameters in both groups compared with baseline values, although this increase was too low to be of any certain clinical significance (**Table 2**). **Figure 1** depicts the change in FVC (L) during treatment with infliximab for each patient.

P-ACE and P-IL-2 are considered markers of activity, and levels are often raised in sarcoidosis patients. These biochemical parameters were therefore monitored during treatment with infliximab. Before infliximab treatment, six patients had increased values of one or both parameters.

Mean P-ACE was 169 U/l before treatment (reference interval 30-115 U/l), 127 U/l at the sev-enth dosage and was normalized (101 U/l) after treatment. Also, mean P-IL-2 was raised be-fore treatment (1,028 kU/l) after the seventh dosage (965 kU/l) and was normalized after treatment (617 kU/l) (reference interval 223-710 kU/l).

Patient 6 was monitored with fluorodeoxyglucose positron emission tomography (FDG-PET) since it was not possible to monitor the activity in any other way. Before infliximab was initiat-ed, this examination showed pathological uptake in both lungs, on the left side around the clavicle, in a retroperitoneal lymph node and in multiple foci in the mediastinum. Regression was seen after 13 treatments with infliximab at which time FDG-PET only revealed pathological uptake in the right lung.

TABLE 2

Mean change in the pulmonary function parameters after seven treatments and at the end of treatment with infliximab compared with the value before treatment. Apart from n, the values are mean ± SD

	Group A[a]		Group B[b]	
	7th treatment	after treatment	7th treatment	after treatment
ΔFEV1				
% of predicted	5.31 ± 5.39	4.19 ± 12.4	3.20 ± 3.94	4.38 ± 12.9
Volume, l	0.20 ± 0.28	0.11 ± 0.42	0.086 ± 0.12	0.15 ± 0.44
ΔFVC				
% of predicted	6.89 ± 5.27	8.34 ± 12.1	5.12 ± 3.80	7.12 ± 11.6
Volume, l	0.34 ± 0.42	0.33 ± 0.61	0.21 ± 0.30	0.35 ± 0.59
n	7	14	5	9
ΔTLC				
% of predicted	1.12 ± 8.12	5.32 ± 5.73	0.90 ± 8.91	5.68 ± 6.76
Volume, l	0.15 ± 0.66	0.32 ± 0.41	0.15 ± 0.71	0.35 ± 0.50
n	6	9	4	6
ΔT_LCO				
% of predicted	–3.56 ± 7.66	6.39 ± 9.14	–1.63 ± 3.20	7.10 ± 7.44
Capacity, mmol/kPa/min	–0.42 ± 0.99	0.63 ± 1.19	–0.14 ± 0.33	0.84 ± 1.06
n	5	9	3	6

FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; n = number of patients; SD = standard deviation; TLC = total lung capacity; T_LCO = diffusion capacity for monoxide.
a) All patients included; b) Patients without pulmonary symptoms (n = 3) and results from the second course of the patients with two treatment courses (n = 2) were left out.

Ocular sarcoidosis

Two patients had chronic, bilateral intermediate uveitis and cystoid macular oedema (CMO) due to sarcoidosis. Ocular inflammation control was primarily achieved with corticosteroids (local and systemic), but relapse occurred after steroid tapering. Because of intolerance to steroids, both patients were subsequently treated with MTX, in one case combined with cyclo-sporine. These were without steroid-sparing effect which was why infliximab was initiated. Ocular inflammation was evaluated by the local ophthalmologists during treatment (vision, slit lamp biomicroscopy, ophthalmoscopy and optical coherence tomography). Both patients responded to infliximab with control of ocular inflammation without need for steroids. Visual acuity during treatment with infliximab was 1.2 bilaterally in one of the patients and 0.8 and 1.0 in the other patient.

Cutaneous sarcoidosis

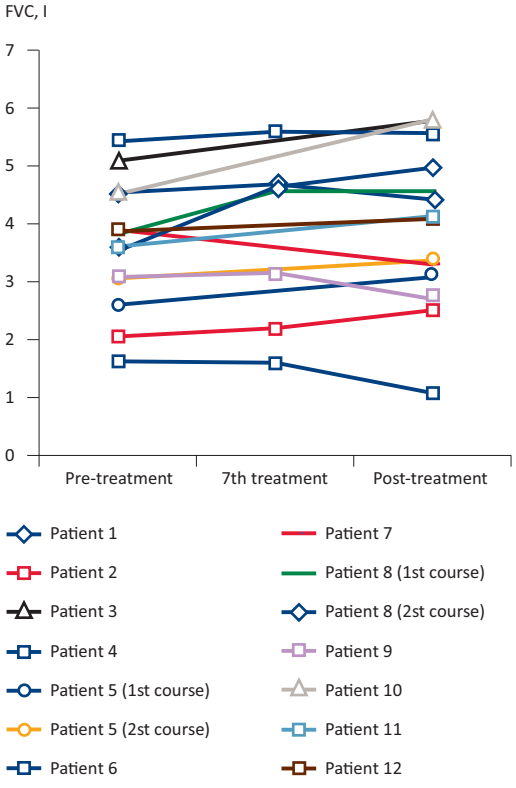
Two patients were treated with infliximab because of refractory cutaneous sarcoid elements.

One patient had multiple, violet and indurated skin elements on the back and the upper extremities. After seven treatments the induration disappeared. After ended treatment, all skin elements disappeared.

The other patient had sarcoid elements on the right cheek and the left knee as well as refractory pulmonary sarcoidosis. The patient received infliximab in two courses. After the first course, the element on the cheek dis-

FIGURE 1

Change in forced vital capacity (FVC) for each patient during treatment with infliximab.



Patients 5 and 8 were treated with infliximab in two courses and they therefore representes twice.
Patient 4, 7 and 12 had extrapulmonary sarcoidosis and were without pulmonary symptoms.

appeared completely, and the element on the knee almost disappeared. Infliximab treatment was ceased for 15 months, but due to recurrence of pulmonary symptoms, decreasing pulmonary function and reappearance of the element on the left knee, infliximab therapy was reinitiated. After only a few dosages, the sarcoid skin elements disappeared.

Miscellaneous

The patients with involvement of the oesophagus, bone marrow, kidney, nose and lymph nodes all experienced reduced symptoms and organ involvement, and all patients reported subjective improvement in symptoms. No side effects were observed.

DISCUSSION

Sarcoidosis is mostly a disease with a benign course, even without treatment. In a few cases, though, a chronic and severe course will develop that does not respond to traditional treat-ments or where side effects are intolerable. Infliximab, a TNF-α inhibitor, is theoretically effective, and beneficial effects of infliximab treatment have been reported.

The effect of infliximab on pulmonary sarcoidosis has been described in three case series [5-7]. A total of six patients with pulmonary sarcoidosis participated in these three case story studies, and they all benefitted from the treatment based on radiographs, subjective symp-toms or spirometry. In our study, nine patients had refractory pulmonary sarcoidosis and an increase in all pulmonary function parameters was seen after treatment. Although the increase was too low to be of any certain clinical significance, an effect was still achieved since their lung function stabilized and did not deteriorate. Moreover, the mean values of P-ACE and P-IL-2 in patients with raised values at baseline (n = 6) normalized after treatment as an expression of decreased disease activity. In one patient, the activity of sarcoidosis was based on FDG-PET. After 13 treatments with infliximab, a distinctly decreased activity uptake was visualized. That FDG-PET can be used as an predictor of activity is supported by a study of Keijsers et al [8] who found that 11 out of 12 patients with sarcoidosis had a decreased activity uptake based on FDG-PET after treatment with infliximab, and a Danish prospective study by Milman et al [9] recently showed similar findings, although in this study, adalimumab, another TNF-α inhibitor, was used.

A weakness in our study is its retrospective design which means that standardization of the treatment course with regard to the supplementary immunosuppressive treatment and the follow-up investigations was not possible. Meanwhile, two randomized, double blinded, placebo-controlled trials have examined the effect of infliximab on pulmonary sarcoidosis [2, 4]. Both found improved lung function after treatment in the infliximab group compared with the placebo group, although this was only significant in the study of Baughman et al [4]. In this study, a post hoc analysis also showed that the effect was more pronounced in patients with more severe sarcoidosis.

Two patients in our study presented with refractory uveitis due to sarcoidosis. After treatment with infliximab (5 mg/kg), both patients achieved control of ocular inflammation without a need for steroids. A similar effect has been shown in several cases series where 17 patients with ocular sarcoidosis participated. [6, 10-14]. All patients achieved control of ocular inflam-mation and/or improvement of vision with infliximab. Two patients ceased treatment due to infliximab side effects.

Cutaneous sarcoidosis was one of the reasons for infliximab treatment in two patients in this study. Both responded to infliximab with a clear regression of the skin elements. This tendency was also observed in other case series [5, 7, 15, 16]. A total of 32 patients with sar-

coid skin elements were treated with infliximab of whom 31 responded with complete resolution or regression of the elements. Only one showed no response, and in one patient treatment was concluded due to side effects to infliximab.

Other TNF-α inhibitors such as adalimumab and etanercept have also been used in the treat-ment of refractory sarcoidosis. Experience with adalimumab remains sparse, but published case studies do indicate that this drug is an efficient treatment in refractory sarcoidosis [9, 17-19]. Furthermore, a recent prospective study showed that adalimumab was effective against refractory uveitis due to sarcoidosis in 22 out of 26 patients after six months of treatment. The remaining four patients showed stabilization of intraocular inflammatory signs [20].

Etanercept treatment in refractory sarcoidosis has been disappointing, possibly due to the dif-ferent targeting of TNF-α, as etanercept is a TNF-α receptor antagonist, while infliximab and adalimumab besides inhibiting the TNF-α receptor also inhibit free TNF-α [2, 3, 18, 19].

CONCLUSION

Infliximab seems to be an efficient and safe treatment in refractory pulmonary and extrap-ulmonary sarcoidosis and in patients with side effects to standard immunotherapy. Our results are in line with other case series which also reported a positive effect of infliximab on refractory sarcoidosis. This is supported by one randomized, double blinded, placebo controlled trial, but more randomized trials are definitely needed. Furthermore, the low number of patients with refractory sarcoidosis treated with infliximab indicates that the treatment must take place in few and highly specialized centres.

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For a complete reference list, please contact the authors.

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