Long-Term Treatment with Infliximab in Patients with Sarcoidosis

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Key Words

Sarcoidosis · Corticosteroids · Tumour necrosis factor- α · Infliximab

Abstract

Background: Long-term benefit and safety of infliximab treatment in patients with chronic sarcoidosis remain unclear. **Objectives:** It was the aim of this study to assess the clinical benefit and safety of long-term infliximab treatment in patients with chronic steroid-resistant sarcoidosis. **Methods:** We conducted a retrospective chart review of all patients with chronic steroid-resistant sarcoidosis who received infliximab between January 2003 and November 2010. Pulmonary function tests and index lesions before and after infliximab therapy were assessed. **Results:** Between January 2003 and November 2010, 28 patients received infliximab, 16 of them for more than 12 months. Five (31%) of these 16 patients with long-term infliximab treatment had a predominantly pulmonary disease, whereas 11 (69%) had a predominantly extrapulmonary involvement. Mean duration of treatment for the 16 patients was 29 months (range 12–62). Six of 11 (55%) patients with mainly extrapulmonary sarcoidosis showed a complete remission of their index lesion, 4/11 (36%) had a partial remission and 1/11 (9%) showed no response. One out of 5 patients with predominantly pul-

monary sarcoidosis showed a >10% improvement in percentage predicted forced vital capacity, 3/5 showed a 0–10% improvement, and in 1/5 patients, percentage predicted forced vital capacity declined during infliximab treatment. Thus, overall, 14/16 (88%) patients profited from long-term infliximab treatment. Suspected adverse effects which lead to a temporary withdrawal of infliximab therapy were noticed in 1/16 (6%) patients. **Conclusions:** This retrospective study indicates that long-term infliximab is very efficient and safe in patients with chronic steroid-resistant sarcoidosis when assessed with individualized treatment targets. Patients with predominantly extrapulmonary sarcoidosis seem to profit more than patients with a predominantly pulmonary disease.

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Introduction

Sarcoidosis is a systemic granulomatous disease that may involve any organ [1–6], but the lungs and lymphatic system are most commonly affected. Although the aetiology of this disease remains unclear, there is evidence for a genetic involvement [3, 7–10], as well as interaction of environmental and genetic factors [3, 8, 11].

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Curative treatment approaches are currently not available, but in the case of chronic and/or progressive sarcoidosis, the administration of corticosteroids is considered standard therapy [6, 12]. Non-steroidal anti-inflammatory agents, cytotoxic or immunomodulatory drugs are appropriate alternatives for patients with intolerable corticosteroid-induced side effects or corticosteroid resistance [12]. However, therapy with these agents is unspecific, the clinical response is variable, and long-term treatment is frequently associated with significant toxicity [13, 14].

Infliximab (Remicade; Centocor, Inc., Malvern, Pa., USA) is a monoclonal antibody that binds to tumour necrosis factor- α (TNF- α), thereby inhibiting TNF- α -induced specific effects. TNF- α plays a pivotal role in the development of non-caseating granulomas which are typically seen in sarcoidosis [2]. Importantly, in patients with active sarcoidosis, the release of TNF- α by activated alveolar macrophages has been documented [11, 15–17], and there is evidence of a correlation between TNF- α release and the progression of sarcoidosis [16, 18]. The efficacy and safety of infliximab treatment in patients with sarcoidosis has been demonstrated previously [12, 19–27], but only recently the first randomized, double-blind, placebo-controlled trials were performed to assess the efficacy of infliximab treatment in patients with chronic sarcoidosis [1, 28, 29]. However, clinical benefit and safety of a long-term targeted therapy with infliximab in patients with chronic sarcoidosis still remain unclear. Here, we present results of a retrospective chart review of patients with chronic progressive, steroid-resistant sarcoidosis treated with infliximab for up to 62 months.

Patients and Methods

Patients

Twenty-eight patients with chronic progressive sarcoidosis received infliximab between November 2003 and November 2010 at the Clinic of Respiratory Medicine, University Hospital Basel, Basel, Switzerland. All 28 patients had histologically confirmed pulmonary and/or extrapulmonary sarcoidosis. Subjects had either steroid-resistant disease, were refractory to steroid-sparing agents, or had developed severe side effects under these treatments. Sixteen of these patients had been treated with infliximab for ≥ 12 months.

All patients had a negative tuberculin skin test and/or a negative blood test (interferon- γ release assay) and showed no signs of chronic and/or serious infections, malignancies and congestive heart failure, respectively.

Approval from the local ethics committee was obtained (Ethics Committee, Faculty of Medicine, University Hospital Basel), and patients provided written informed consent.

Infliximab Treatment

All patients received intravenous infusions of infliximab, typically 3 mg/kg, in 4-/6-/8-weekly intervals. However, during the infliximab treatment period, patients remained on their concomitant medication with oral corticosteroids and/or other immunomodulatory drugs, at a minimum dose of typically 5 mg prednisone and 50 mg of azathioprine per day.

During the whole treatment period, all patients were seen on a regular basis by a senior physician in the out-patient clinic of the University Hospital Basel, Basel, Switzerland. Treatment response and adverse events were monitored and documented continually. Patients who continued the infliximab treatment beyond the end of the observation period (November 2010) were regularly monitored to date.

Outcome Measures

The organ in which sarcoidosis lead to the greatest negative impact on clinical function and quality of life was identified for each patient as index organ, and outcome measures were individualized accordingly: (1) in patients with predominantly lung involvement, forced vital capacity (FVC) and percentage predicted FVC (FVC,%P) were assessed before and after infliximab treatment; (2) in patients with predominantly extrapulmonary sarcoidosis, response to infliximab treatment was assessed as complete remission, partial remission or no response of the index organ; decision on treatment response was reached interdisciplinary. Assessments of neurological deficit, involvement of the skin and heart were performed by sarcoidosis experienced neurologists, dermatologists and cardiologists, respectively.

Results

Baseline Characteristics and Patient Disposition

A total of 28 patients with chronic progressive, steroid-resistant sarcoidosis were treated with infliximab between November 2003 and November 2010. Among these 28 patients, 16 had been treated for ≥ 12 months and were thought eligible for this study (fig. 1). According to their index organ, there were 5 (31%) patients with predominantly pulmonary involvement and 11 (69%) patients with predominantly extrapulmonary disease (fig. 1). Two of the 5 patients with predominantly pulmonary disease suffered from sarcoidosis stage II according to Silzbach and 3 patients from Silzbach stage IV. A disposition according to the index organ of patients with predominantly extrapulmonary disease is shown in figure 1 (upper part). The baseline characteristics of all patients treated for ≥ 12 months are listed in table 1. The mean duration of treatment was 29 months (range 12–62). The disposition according to the index organ of those 12 patients with <12 months of treatment and reasons for withdrawal of infliximab therapy are shown in figure 1 (lower part).

Fig. 1. Disposition of patients with chronic steroid-resistant sarcoidosis and long-term infliximab treatment according to their predominantly involved organ (upper part), and course of patients with <12 months of infliximab treatment (n = 12; lower part). CNS = Central nervous system.

Change from Baseline in Lung Function Parameters

Compared to baseline, 1/5 patients with predominantly pulmonary sarcoidosis showed a >10% improvement in FVC,%P (fig. 2a, continuous line), and 3/5 patients showed a 0–10% improvement after infliximab therapy (dashed lines). In 1/5 patients with predominantly pulmonary sarcoidosis, FVC,%P declined during infliximab treatment (dotted line). The mean improvement in FVC,%P was 6% (range –6 to 23). At baseline, absolute FVC values ranged from 0.94 to 3.63 litres (mean 2.26 ± 1.25 ; fig. 2b). After infliximab treatment, absolute FVC values ranged from 0.77 to 4.28 litres, with the mean FVC slightly increasing to 2.57 ± 1.58 litres.

Response in Patients with Predominantly Extrapulmonary Sarcoidosis

Of the 11 patients with predominantly extrapulmonary sarcoidosis, 10 (91%) responded to infliximab treatment. Six out of 11 (55%) patients showed a complete remission of their index lesion, and 4/11 (36%) had a partial remission (table 2). In 1/11 (9%) patients, no response could be observed (table 2).

Table 3 shows the response of the index organ of each patient with predominantly extrapulmonary sarcoidosis and the respective duration of infliximab treatment. Based on clinical assessments, patient No. 15 had a partial remission of her neurologic impairment 3 months after

Fig. 2. a FVC,%P at baseline and after infliximab treatment for each patient with predominantly pulmonary sarcoidosis (n = 5). **b** FVC at baseline and after infliximab treatment for each patient with predominantly pulmonary sarcoidosis (n = 5).

Fig. 3. Gadolinium-enhanced MRI of patient No. 15. Axial T₁-weighted images (TR/TE, 663/17 ms) after intravenous administration of contrast agent (Magnevist at a dose of 0.1 mmol/kg; Bayer Schering Pharma, Berlin, Germany). Multiple gadolinium-enhancing white matter lesions consistent with an active inflammatory process are predominantly present in the left hemisphere at baseline examination (**a**, arrowheads). Most lesions – except for one (**b**, arrowhead) – completely resolved at follow-up MRI examination obtained 3 months after the start of infliximab treatment (**b**).

the start of infliximab treatment, and a follow-up magnetic resonance imaging (MRI) examination of the brain was performed. Figure 3 shows improvement in gadolinium-enhancing white matter lesions after 3 months of infliximab treatment.

Adverse Events

Fifteen out of 16 (94%) patients tolerated long-term infliximab treatment without any clinically relevant side effects. A possible adverse event occurred in 1/16 (6%) patients: after more than 4 years of well-tolerated infliximab treatment, the patient suffered from a symptomatic bradyarrhythmia 6 h after infliximab infusion. A cardiac involvement of sarcoidosis had not been suspected by then, and an MRI of the heart showed no evidence of myocardial granulomas – a myocardial biopsy was not performed. Due to persistent symptomatic bradyarrhythmia, a pacemaker had to be implanted. Whether the observed arrhythmia was due to infliximab treatment or whether it was a symptom of cardiac involvement of the systemic disease was not clearly evident, and infliximab therapy was continued thereafter without recurrence of cardiac symptoms.

None of the 16 patients developed severe infections or malignancies during infliximab therapy.

Discussion

In a prior randomized, double-blind, placebo-controlled trial, infliximab therapy has been demonstrated to cause a significant improvement in FVC,%P, as well as an improvement in extrapulmonary symptoms in patients with chronic sarcoidosis [1, 29]. However, the study is limited by therapy duration of only 24 weeks, and fur-

Table 1. Baseline demographics, disease characteristics and concomitant medication of patients with long-term infliximab treatment

Characteristics	n = 16
Age, years	51 ± 13 [30–76]
Female/male	8/8
Race: White/Black/Asian/other	16/0/0/0
Extrapulmonary involvement	11 (69)
Years since histologically proven sarcoidosis	12 ± 9 [3–38]
Concomitant medication	
Corticosteroids only	6 (37)
Immunomodulator only	0
Corticosteroid + immunomodulator	7 (44)
None	3 (19)

Values are means ± standard deviations, with ranges in brackets. Figures in parentheses are percentages.

Table 2. Treatment responses for patients with predominantly extrapulmonary sarcoidosis (n = 11)

Complete remission	6 (55)
Partial remission	4 (36)
No response	1 (9)

Figures in parentheses are percentages.

Table 3. Index organ and treatment response achieved during the respective duration of infliximab treatment for each patient with predominantly extrapulmonary sarcoidosis (n = 11)

Patient No.	Index organ	Response	Duration of therapy months
1	CNS	complete remission	59
2	CNS	partial remission	49
3	CNS	complete remission	17
4	lupus pernio	partial remission	31
5	lupus pernio	complete remission	62
6	lupus pernio	complete remission	20
7	CNS	complete remission	56
8	CNS	no response	13
11	heart	partial remission	13
15	CNS	partial remission	24
16	lupus pernio	complete remission	33

Numbering of patients according to the start date of infliximab treatment. CNS = Central nervous system.

ther data about efficacy and safety of long-term infliximab treatment are scant. Therefore, our study with a mean duration of 29 months might give additional information for the use of infliximab in the clinical practice.

Sarcoidosis is a heterogeneous disease, and thus, responses to treatment are heterogeneous too. In this study, an index organ was identified for each patient, and outcome measures were individualized accordingly. In patients with predominantly extrapulmonary involvement, the outcome measure was defined as the extent of benefit with regard to the specific organ impairment at baseline. We acknowledge that this assessment of treatment response was not standardized and/or validated. However, medical examinations before, during and after infliximab treatment were performed by (at least) two specialists from different subspecialties who were experienced in the clinical presentation and management of sarcoidosis patients, and thus, the decision on treatment response was reached interdisciplinary. Previously designed tools to assess extrapulmonary organ involvement [29–31] have not been validated and/or standardized for the European population either, and thus, a validated and standardized tool to assess whether and to what extent an extrapulmonary organ is involved is still elusive. Our observation that 91% of patients with predominantly extrapulmonary sarcoidosis responded to infliximab treatment is in line with previously published data from case reports, retrospective chart analysis and non-randomized studies that demonstrated a high efficacy of infliximab for patients with refractory extrapulmonary sarcoidosis [5, 12, 19–21, 23, 25–27, 29, 32–35]. Importantly, our findings are supported by recently published data from a double-blind, randomized study demonstrating that infliximab therapy improved extrapulmonary sarcoidosis compared with placebo [29].

The observed mean improvement in FVC,%P of 6% in patients with predominantly pulmonary involvement was considerably greater than the improvement in FVC,%P observed in the randomized, placebo-controlled trial by Baughman et al. [1] (2.5% improvement in FVC,%P). A possible explanation for this discrepancy might be the fact that only patients with stable pulmonary disease were included in the study of Baughman et al. [1], whereas our study group was comprised of patients with unstable and progressive disease. A comparison of baseline FVC values between the two study groups supports this assumption. It has been suggested by Baughman et al. [1] that by studying only patients with stable disease, background therapy may have diminished the response to infliximab therapy, and exploratory analyses

revealed that patients with more severe disease were more likely to benefit from infliximab therapy [1]. We acknowledge that the clinical importance of a 6% FVC,%P improvement is unclear, and additional assessment of quality of life or exercise testing would be mandatory in future studies.

In this study, infliximab had to be withdrawn temporarily in only 1/16 (4%) patients due to suspected adverse effect, and thus, the incidence is comparable with the one observed in the study by Baughman et al. [1] (5.5%). Symptomatic disorders of cardiac rhythm associated with the use of infliximab have been reported previously [36, 37], but in our patient, cardiac involvement of the systemic disease was not excluded. In summary, infliximab treatment was well tolerated, and – even after long-term treatment – no cases of malignancies or severe infections such as tuberculosis or pneumonia occurred.

In conclusion, an analysis of this follow-up study indicates that long-term infliximab is very efficient in patients with steroid-resistant sarcoidosis when assessed with individualized treatment targets. Patients with predominantly extrapulmonary sarcoidosis seem to profit more than patients with predominantly pulmonary disease. Importantly, this observation is supported by results from a post hoc analysis within the randomized placebo-controlled trial of Baughman et al. [1] which suggested that infliximab therapy might be more beneficial

in patients with multi-organ extrapulmonary involvement. Furthermore, our data suggest that in patients with chronic steroid-resistant pulmonary and/or extrapulmonary sarcoidosis, infliximab treatment is well tolerated and safe, even after long-term application. We believe that this retrospective analysis provides further evidence for a substantial clinical benefit of infliximab treatment in these patients, i.e. infliximab seems to be a valid option as second-/third-line therapy for patients with refractory – specifically extrapulmonary – sarcoidosis already receiving corticosteroids and/or other immunomodulatory agents. Further large, randomized and controlled studies with standardized assessment criteria and long-term drug administration are needed to evaluate the efficacy and safety of infliximab in patients with chronic sarcoidosis.

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Financial Disclosure and Conflicts of Interest

The authors have no conflicts of interest to disclose.

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