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ORIGINAL COMMUNICATION

Long-term outcomes of refractory neurosarcoidosis treated with infliximab

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Abstract Central nervous system localizations of sarcoidosis may be refractory to conventional treatment such as steroids and immunosuppressive drugs. Infliximab, a TNF-α antagonist chimeric antibody, has been shown to be effective for treatment of these localizations. The aim of this study was to evaluate the efficacy and safety, in particular the long-term outcomes, of the use of infliximab for the treatment of neurosarcoidosis. We retrospectively reviewed medical records of patients with neurosarcoidosis who had been treated with infliximab between 2009 and 2015. All patients had histologically proven non-caseating granulomas. Eighteen patients with histologically proven sarcoidosis were included in this study. All had neurological involvement consisting of meningeal ($n = 16$), cerebral ($n = 10$), spinal cord ($n = 6$), and/or optic nerve ($n = 5$) involvement. Sixteen patients had previously received at least one immunosuppressive drug in addition to corticosteroids, including cyclophosphamide in 11 patients. All patients received treatment with infliximab (3–7.5 mg/kg) associated with corticosteroids ($n = 18$), low-dose methotrexate ($n = 15$), azathioprine ($n = 2$), or mycophenolate ($n = 1$). Sixteen out of 18 patients improved clinically (initial median modified Rankin scale score of 3, final median score of 1; $p < 0.0001$). At 6 months after initiation of infliximab, six patients obtained complete remission (33%), ten attained partial remission (56%), and two had stable disease (11%). The median follow-up time was 20 months (range 6–93). Nine patients relapsed during follow-up (50%). Eight patients developed toxic side effects and seven of these side effects were infectious events. Infliximab is an efficacious treatment of refractory neurosarcoidosis. However, relapses frequently occurred during follow-up.

Keywords Neurosarcoidosis · Infliximab · Relapses · Side effects

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Introduction

Sarcoidosis is a multi-systemic granulomatous disease of unknown cause characterized by the infiltration of the tissues by non-caseating granulomas. It can affect various organs and may remit spontaneously, although it can also be chronic or progressive in up to 25% of patients [21]. Clinical involvement of the nervous system occurs in approximately 5% of cases and may affect virtually any part of the peripheral (PNS) or central nervous system (CNS) [6, 8, 12, 13].

Corticosteroids are the drug of choice for managing neurosarcoidosis, but they may not be effective in some cases. A second-line immunosuppressive treatment (e.g., methotrexate (MTX), mycophenolate mofetil (MMF), or azathioprine (AZA)) may be used, although this may also be insufficient [2]. Most of the drugs used for sarcoidosis target tumor necrosis factor (TNF)-α, which plays a crucial role in the initiation and development of the granulomatous process. Indeed, sarcoidosis is a Th1-Th17 disease leading to TNF-alpha synthesis by activated macrophages [5]. The efficacy of TNF-α antagonists has been reported in the literature for the treatment of pulmonary and extrapulmonary sarcoidosis, especially in patients who are refractory to corticosteroid therapy [1, 9]. Infliximab is a chimeric immunoglobulin G monoclonal antibody directed against TNF-α that has been used in a randomized, double-blinded, placebo-controlled trial studying chronic corticosteroid-dependent pulmonary sarcoidosis. The effect of infliximab on extrapulmonary sarcoidosis organ involvement has also been reported in this trial, as well as in several case reports and small open-labeled series [9, 14]. However, the long-term outcomes of patients with neurosarcoidosis treated with infliximab have not been reported. Thus, we conducted a retrospective multicenter study to evaluate the efficacy of infliximab for remission induction and long-term remission maintenance in patients with neurosarcoidosis and also to assess the tolerance of this drug.

Patients and methods

Patient selection and inclusion criteria

This is a retrospective multicenter study conducted at two University Hospitals and one general hospital from 2010 to 2015. Patients with a definite or probable diagnosis of neurosarcoidosis who received at least one infusion of infliximab were included [23]. The following criteria were used to diagnose neurosarcoidosis: (1) presence of clinical neurological signs, (2) compatible clinical, cerebro-spinal fluid analysis and radiological features, (3) presence of nervous system (definite) or extra-nervous system (probable) non-caseating granulomas, and (4) exclusion of differential diagnoses.

The study was conducted in compliance with the Good Clinical Practice protocol and the Declaration of Helsinki principles and was approved by the Institutional Review Board CPP Ile de France VI.

Patient's characteristics

Clinical, biological, and imaging data were retrospectively collected by practitioners in charge of the patients and were centrally reviewed by FCA. Baseline is defined as the time of initiation of infliximab. The modified Rankin scores were determined retrospectively at baseline and at the end of follow-up. Follow-up ended in December 2015.

Efficacy and tolerance

A complete neurological remission was defined by a neurological-related extra-pulmonary physician organ severity tool (ePOST) score of 0. The ePOST score is the sum of 17 extra-pulmonary organ activity scores ranging from 0 to 6 (from no activity to maximal activity) [9]. Thus the neurological-related ePOST score ranges from 0 to 6. A partial neurological remission was defined by an improvement of at least 1 point of the neurological-related ePOST score. The stability of neurological involvement was defined by the absence of modification of the ePOST score. Progression of the neurological involvement was defined by an increase of at least 1 point of the neurological-related ePOST score. The same definitions were applied for the global ePOST score (17 extra-thoracic organs).

A relapse was defined by an increase of at least 1 point of the ePOST score after a partial or complete remission (which corresponds to recurrence or occurrence of a new localization attributable to sarcoidosis). A relapse was classified as a neurological or extra-neurological depending of the modification of the neurological or extra-neurological ePOST scores.

The primary endpoint was the number of complete or partial remissions at 6 months' follow-up. The secondary endpoint was the number of complete or partial remission at the end of the follow-up. The number of relapses was noted for each patient. All side effects were noted.

Statistical analysis

Data are presented as the median and range for continuous variables and as the number and percentage for categorical variables. Modified Rankin scores and daily steroids doses were compared between baseline and the end of follow-up using Wilcoxon and Mann–Whitney test, respectively. Statistical analyses were performed using the GraphPad Prism v 6.0 (GraphPad Software, La Jolla, CA, USA).

Results

Patient characteristics before infliximab initiation

The characteristics of the patients are reported in the Table 1.

Eighteen patients (11 males, 7 females) were included in the study. The median age at the time of sarcoidosis

Table 1 Demographic and clinical characteristics of the 18 patients

Patient	Sex, age[a]	Sarcoidosis involvements (type of CNS involvement)	Type of TNF-α antagonist treatment (dosage, mg/kg)	Duration of TNF-α antagonist treatment (months)	Relapse(s) [*n*, localizations of the relapse(s)]	Side effect(s)	Concomitant treatments (all had corticosteroids)
#1	M, 32	T, S, O, E (M, C, ON)	Infliximab (5 then 3)[b]	93	0	0	MTX 10 mg/week
#2	M, 29	T, O, H (M, CN)	Infliximab (5)[b]	20	1 (after withdrawal), CNS	Pulmonary infection	MTX 10 mg/week
#3	F, 34	T (M, C, E, ICH)	Infliximab (5)[b]	45	2, CNS	Pulmonary infection	MTX 10 mg/week
#4	F, 45	T, E (M, C, E, CN)	Infliximab (5)[b]	56	2, CNS	Pulmonary infection	MTX 10 mg/week
#5	F, 30	T, S, E (C, CN)	Infliximab (5)[b]	56	1, lung and skin	Pulmonary infection	MTX 10 mg/week
#6	M, 58	T, S (M, C, Med)	Infliximab (5 then 7.5)	12[c]	1, CNS (after withdrawal)	0	MTX 10 mg/week
#7	M, 49	T, O (ON)	Infliximab (5) then adalimumab[b]	48	1, ocular	0	MMF 2 g/day
#8	F, 46	T, S, O, H (M, Med, R, ON)	Infliximab (5)[b]	17	0	Cutaneous abcess	MTX 10 mg/week
#9	M, 39	T, H (M, C, E)	Infliximab (5)[b]	20	1, CNS	0	MTX 10 mg/week
#10	F, 48	T (M, Med, CN)	Infliximab (5)[b]	11	0	0	MTX 10 mg/week
#11	M, 37	T (M, C, E, Med)	Infliximab (5)[b]	18	0	0	MTX 10 mg/week
#12	F, 51	T, S, E (M, C, E)	Infliximab (5 then 3)[b]	72	3 (after withdrawal), multisystemic	0	MTX 10 mg/week then leflunomide
#13	M, 27	T, E (M, C, CN, ON)	Infliximab (5)[b]	31	0	0	AZA 1 mg/kg/day
#14	M, 39	T, O, E (M)	Infliximab (5)[b]	30	7 (after withdrawal), CNS + O	Pulmonary infection	MTX 20 then 10 mg/week then AZA 2 mg/kg/day
#15	F, 37	T (M, Med, R)	Infliximab (3)[b]	15	0	CMV infection	MTX 10 mg/week
#16	M, 33	T (M, C, E)	Infliximab (7.5)[b]	13	0	0	AZA 1 mg/kg/day
#17	M, 39	O, E (M, ON)	Infliximab (5) then adalimumab[b]	12	0	Alopecia	MTX 10 mg/week
#18	M, 30	T, E (M, E, Med)	Infliximab (5)[b]	6	0	0	MTX 10 mg/week

AZA azathioprine, *MMF* mycophenolate mofetil, *MTX* methotrexate, *T* thoracic, *S* skin, *O* ophthalmologic, *E* ear-nose-throat, *H* heart

For CNS involvement *M* denotes meningeal involvement, *C* cerebral, *Med* medullar, *R* radiculopathy, *CN* cranial nerves (other than optic nerves), *ON* optic nerves, *E* epilepsy, *ICH* intracranial hypertension

[a] Age at sarcoidosis diagnosis

[b] Patient still treated at the end of follow-up

[c] Dead during follow-up (after infliximab discontinuation)

diagnosis was 38 years (range 27–51). Neurological manifestations consisted of meningeal involvement ($n = 16$), cerebral localization ($n = 10$), cranial nerves involvement ($n = 9$), myelitis ($n = 6$), and radicular infiltration ($n = 2$). Seven patients had epilepsy, and one had intracranial hypertension. Additionally, five patients had pituitary involvement. Five patients had optic nerve involvement.

Sarcoidosis involved mainly the lungs and/or mediastinal lymph nodes ($n = 17$), peripheral lymph nodes

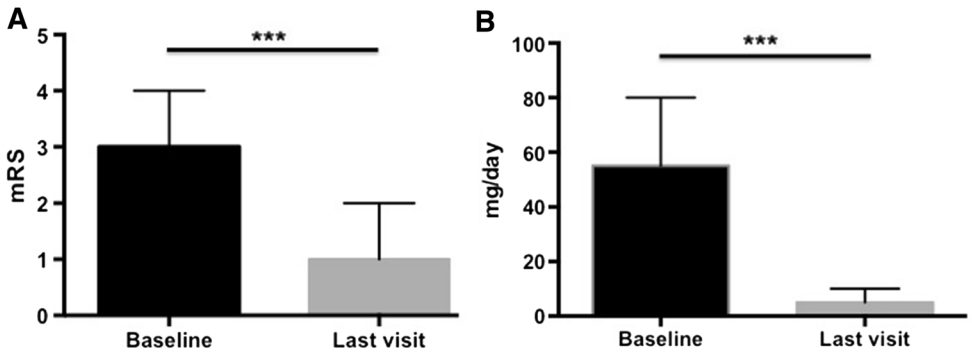

Fig. 1 Efficacy of TNF-alpha antagonists. Modified rankin scores (**a**) and corticosteroid dosages (**b**) at baseline and at the end of follow-up. Medians with IQR are plotted. *mRS* modified rankin scale, *IQR* interquartile range

($n = 12$), ear-nose-throat (ENT) ($n = 8$), eyes ($n = 6$), skin ($n = 5$), and heart ($n = 3$). Ten patients had stage I and seven patients had stage 2 disease based on chest X-ray findings.

Sixteen patients had an extra-neurological histological proof of non-caseating granulomas, obtained from lymph nodes ($n = 6$), bronchial tissue ($n = 4$), skin ($n = 4$), minor salivary gland ($n = 3$), and/or ENT tissues ($n = 2$) (some patients had several biopsies). Additionally, two patients had histologically proven non-caseating granuloma obtained from CNS tissue (meningeal tissue from spinal and optic nerve localizations, respectively).

Before receiving infliximab, all patients had been treated with steroids in association with at least one immunosuppressive drug in 16 patients: cyclophosphamide (CYC) ($n = 11$), MTX ($n = 10$), MMF ($n = 3$), hydroxychloroquine (HCQ) ($n = 1$) or cyclosporine ($n = 1$). The median number of lines of immunosuppressive therapies, in addition to steroids, before infliximab was 1.5 (range 0–3). The median duration of treatment before infliximab therapy was 24 months (ranging from 1 to 60).

Infliximab treatment

Infliximab was initially administered intravenously at a dose of 5 mg/kg in 16 patients, 3 mg/kg in one patient, and 7.5 mg/kg in one patient. Initially, all patients received two infusions given at 2-week intervals, then 15 patients received an infusion every 4 weeks during the first 6 months, and two patients received infusions every 6 weeks. One patient developed a severe cutaneous side effect after the administration of two infliximab perfusions and was subsequently switched to adalimumab. After the first 6 months, the interval between infusions was heterogeneous and varied between 4 and 8 weeks (median 6 weeks). An additional patient was switched to adalimumab after six infliximab infusions.

Infliximab was administered in combination with low-dose MTX (7.5–20 mg/week; median dose 10 mg) in 15 patients. One patient received combined therapy with MMF 2 mg/day, and two patients received a 1 mg/kg/day AZA treatment in addition to infliximab. All patients received corticosteroids during infliximab treatment.

At 6 months after baseline, 6 (33%) patients had complete neurological remission, 10 (56%) had partial neurological remission, and 2 (11%) were stable. Overall, partial or complete remission was obtained in 16 (89%) patients with a statistically significant decrease in the daily steroid dose (median daily dose at baseline was 50 mg/day and at the last visit, it was 5 mg/day, $p < 0.0001$) (Fig. 1). A significant decrease in the modified Rankin score was also observed (from 3 at baseline to 1 at the last visit, $p < 0.0001$) (Fig. 1).

Follow-up

The median follow-up time was 20 months (range 6–93). TNF-alpha antagonist treatment was discontinued in four patients due to an absence of efficacy ($n = 1$, patient #6, this patient had been considered as "stable", without clinical improvement), complete remission without disease activity ($n = 2$, patients #12 and #14), or loss to follow-up ($n = 1$, patient #2).

During infliximab treatment, five of 14 (36%) patients relapsed during the follow-up period and 4/4 (100%) after infliximab withdrawal (relapse in three and disease progression in one). Among the five patients who relapsed during infliximab treatment, three had a CNS flare, one had an ophthalmologic flare, and one had a lung and skin flare. Relapses occurred when the interval between the infusions was 5 or 6 weeks. Patients with a relapse were treated by increasing the daily steroid dose and decreasing the interval between infliximab perfusions. Among the four patients who relapsed after infliximab discontinuation (patients #2, #6, #12, #14), improvement occurred after the infliximab treatment was resumed in three of them (the patient #6 who experienced a disease progression was not re-treated with infliximab). Among these four patients, the flare consisted of multisystemic disease for two patients and a CNS flare or progression for two.

At the end of the follow-up, 16 patients (89%) were still being treated with TNF-α antagonists (14 with infliximab and two with adalimumab). One patient died (#6), and another was lost to follow-up (#13). At the end of follow-up, five patients had a complete remission (31%), ten had a partial remission (63%), and one was stable (6%). Patient #6 died during follow-up of unknown cause (sudden death without an autopsy) after infliximab interruption (for absence of efficacy) and despite steroid and MMF treatment. As shown in the Fig. 1, the median daily steroid dose at the end of follow-up was 5 mg (0–12.5 range) that was significantly lower than the dose at the beginning of treatment.

Safety

Eight patients experienced toxic side effects. Infectious events occurred in seven patients (39%) consisting of: pulmonary infections requiring hospitalisations ($n = 5$, 4 without bacteriologic documentation, 1 with *Pseudomonas aeruginosa* and atypical mycobacteria), cellulitis ($n = 1$), and cytomegalovirus primo-infection with fever, and cytolysis ($n = 1$). All but one infectious adverse events occurred during the first year of infliximab treatment. Additionally, one patient developed severe alopecia that required infliximab interruption (this patient was subsequently treated with adalimumab).

Discussion

This multicenter, collaborative study reports the efficacy of infliximab for the management of neurosarcoidosis with a focus on long-term outcomes. Infliximab displayed a high rate of efficacy (89%), although sometimes it is given as a 4th line immunosuppressive therapy. However, the results from this study show a high rate of relapse (50%) during follow-up, including patients who were receiving TNF-α antagonist treatment (35%), and despite maintenance therapy in others. The safety profile of infliximab for management of neurosarcoidosis was marked by the occurrence of infectious events (39%), possibly facilitated by a history of several lines of immunosuppressive treatments more than cumulative infliximab treatment.

Infliximab is increasingly prescribed for neurosarcoidosis [7]. In a prospective randomized placebo-controlled study, 13 patients who received infliximab had nervous system involvement, while 7 patients who received placebo had nervous system involvement [9]. The patients received corticosteroids in the two arms of the study. Two patients in the infliximab group had a complete remission at W24 compared with 0 in the placebo group. There were no details provided regarding the neurological ePOST scores. The efficacy of infliximab has also been studied in small series and case reports of patients with neurosarcoidosis (Table 2) [3, 4, 10, 11, 14–20].

Thirty-eight cases with biopsy-proven neurosarcoidosis treated with TNF-alpha antagonists have been reported so far (excluding patients with non-histologically proven sarcoidosis and those from studies which did not focus on neurosarcoidosis). Infliximab has been shown to demonstrate short-term efficacy in these patients, even in case of previous immunosuppressive drugs failure, as we observed in our study. Of note, other immunosuppressive drugs

Table 2 Results of previously published cases of biopsy-proven neurosarcoidosis treated with TNF-alpha antagonists (cases without histology were not included, as well as those from studies not focusing on neurosarcoidosis)

	$n = 38$ cases
Age (mean, range)	41.7 years (22–74)
Sex ratio (M/W)	20 W/18 M
Neurological involvement (*n*, %)	
Cerebral or meningeal	27 (71%)
Myelitis	14 (37%)
Cranial nerves	10 (26%)
Optic nerves	5 (13%)
Extra-neurological localizations	
Thoracic (lung or lymph nodes)	27/32 (84%)
Eyes	2/32 (6%)
Sinus	2/32 (6%)
Previous treatments (*n*, %)	
Corticosteroids	38 (100%)
Methotrexate	13 (34%)
Mycophenolate mofetil	6 (16%)
Cyclophosphamide	10 (26%)
Azathioprine	10 (26%)
Ciclosporin	2 (5%)
Leflunomide	1 (3%)
Plasmatic exchange	1 (3%)
Type of TNF-alpha antagonists (*n*, %)	
Etanercept	1 (before infliximab)
Adalimumab	1 (+1 after infliximab)
Infliximab	36 (95%)
Reason for TNF-alpha antagonist treatment	
Previous treatments failure	35 (92%)
Previous treatments intolerance	1 (CYC induced alopecia)
Steroid-sparing effect	2 (5%)
Efficacy[a]	38 (100%)

CYC cyclophosphamid

[a] Efficacy rate could have been influenced by a publication bias

(methotrexate, azathioprine, etc) given concomitantly to TNF-alpha antagonists may have biased the evaluation of their efficacy. Relapse rates after infliximab withdrawal were high, as previously reported [22]. However, our study also demonstrated a high relapse rate even during TNF-alpha antagonist treatment. This may be due to the blood–brain barrier leading to high rate of relapses even during infliximab treatments. These relapses occurred after increasing the time interval between infusions, suggesting that a regimen of 5 mg/kg infusion administered every 4 weeks could be maintained for a long time for CNS sarcoidosis patients. We did not have any information about neutralizing antibodies against infliximab in our patients, in particular among those who relapsed.

Our study has several limitations. The retrospective design and absence of placebo-arm does not allow us to give high-level evidence conclusions about the efficacy of infliximab. However, due to the severity of disease in these patients, a placebo-controlled trial does not seem ethically possible. In particular, 11 patients had previously received a CYC treatment in our series. Another limitation for the interpretation of data, in particular the rate of relapse, is that the infliximab dosage and interval between perfusions were heterogeneous. Finally, some side effects may have not been recognized or noted due to the retrospective study design.

In conclusion, administration of infliximab seems to be an efficacious treatment for refractory neurosarcoidosis but has a high rate of relapses. Prospective studies to examine combined therapies and treatment duration should be considered, despite the small number of patients.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest and no disclosures relevant to the manuscript. This work did not receive any funding.

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