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ORIGINAL COMMUNICATION

Adalimumab for CNS sarcoidosis: single-center experience and literature review

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Abstract

Background Tumor necrosis factor (TNF) alpha is critical in the development of granulomas and multiple recent reports have highlighted the role of infliximab, an infused TNF alpha inhibitor, in the treatment of neurosarcoidosis. As a self-injected TNF alpha inhibitor, adalimumab has certain advantages over infused medications, including greater patient freedom and autonomy. Experience with adalimumab is not well reported in the literature.

Objective To report clinical experience with adalimumab in the treatment of central nervous system (CNS) sarcoidosis by combining observations in our center with those that have been reported in the literature.

Methods Patients were identified from the Mass General Brigham Research Patient Data Registry and in the literature by searching PubMed. Patients with CNS manifestations of sarcoidosis treated with adalimumab were included for retrospective review and analyzed for baseline characteristics, treatment indications, outcomes, and adverse effects.

Results Adalimumab was commonly started after failure of or intolerance to infliximab and methotrexate. Of those with adequate follow-up, 5/10 ultimately improved, remission was maintained in 3/10, and 2/10 with active disease remained stable without further worsening. One patient suffered a relapse, likely multifactorial in etiology, but has remained relapse free on adalimumab for 10 months subsequently. Three patients ultimately discontinued adalimumab.

Conclusions Preliminary evidence suggests that adalimumab may be a reasonable therapeutic option for patients with neurosarcoidosis affecting the CNS, including those with medically refractory disease.

Keywords Neurosarcoidosis · Adalimumab · Humira · TNF alpha inhibitor (TNFi) · CNS sarcoidosis

Introduction

Sarcoidosis is a systemic multi-organ auto-inflammatory disease characterized pathologically by non-caseating granulomas and frequently involves the central nervous system (CNS) or peripheral nervous system (PNS) [1]. The inflammatory cytokine tumor necrosis factor alpha (TNF alpha) is pivotal for the development and maintenance of granulomas. Evidence in the form of multi-center case series has demonstrated the effectiveness of infliximab, a TNF alpha inhibitor, in the management of challenging neurosarcoidosis cases [2, 3]. There is now general expert consensus regarding the use of infliximab for this indication [3].

Infliximab is an intravenous (IV) medication commonly administered every 4–8 weeks [4]. As a part of this regimen, patients commit to frequent visits to an infusion center or welcome infusion companies into their homes for treatment. In low resource settings and especially in rural communities, the logistical difficulty of traveling to a site to receive care potentially represents an obstacle for treatment. Intravenous infusions can also be a challenge for patients if venous cannulation proves difficult, which may necessitate port placement in some cases.

Adalimumab, another TNF alpha inhibitor in routine clinical use for a number of rheumatologic conditions, is a potential alternative to infliximab and offers several practical and logistical advantages over IV treatments. Patients are able to administer adalimumab to themselves subcutaneously at any location, thereby preserving patient autonomy

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[4]. The benefits of self-injectables have also played a significant role in reducing healthcare exposures and treatment interruptions during the current COVID pandemic, for instance.

Adalimumab has been noted to be beneficial for patients with systemic sarcoidosis intolerant to infliximab and as a supplement to methotrexate in cardiac sarcoidosis [5–7]. Thus far, however, only four clear cases of neurosarcoidosis treated with adalimumab have been described, at least three of which had favorable outcomes [8, 9]. In this retrospective case series and literature review, we combine our experience in seven patients with that of the four patients described in the literature to explore the clinical efficacy and application of adalimumab for the treatment of CNS neurosarcoidosis specifically. In this descriptive series, we endeavor to clarify clinical scenarios that might prompt its use, dosing regimens and concomitant immunosuppressive agents, and treatment outcomes based on clinical and radiographic response, relapses, and adverse effects.

Methods

Patient cohort

All patients with electronic medical records seen within the Mass General Brigham (MGB) hospital system are included in its Research Patient Data Registry (RPDR). The RPDR was searched for the following terms, chosen to be inclusive of all known possible clinical phenotypes of neurosarcoidosis involving the CNS: "sarcoid meningitis," "multiple cranial nerve palsies in sarcoidosis," "sarcoidosis of other sites," and "meningitis in sarcoidosis." Patients presenting to an MGB facility during the period between 1/1/2000 and 6/30/2020 (date of censoring) were included in the initial patient query. Patient charts then underwent screening to determine if they had an exposure to adalimumab, and those that had were further evaluated to determine if they met inclusion criteria with no cause for exclusion.

Inclusion criteria

Patients were considered to have neurosarcoidosis if they met criteria for either a "definite" or "probable" diagnosis on the basis of the Neurosarcoidosis Consortium Consensus Group's 2018 Diagnostic Criteria [10]. A definite diagnosis of neurosarcoidosis is defined as having consistent neuropathology in the setting of a fitting clinical picture, while a probable diagnosis is established by extra-neural pathology [10]. Patients with "possible" neurosarcoidosis (no pathology from any tissue) were included on a case-by-case basis and only if the clinical and imaging features were stereotypical for neurosarcoidosis, a biopsy was not pursued on account of unacceptable risk to the patient, and there was thorough exclusion of possible alternative etiologies [10]. Patients were additionally only included if the indication for adalimumab was specifically for management of the neurologic component. Only patients with sarcoidosis involving the CNS were included since that is the primary scenario in which TNF alpha inhibitors are considered for use.

Exclusion criteria

Given that the primary focus of this study is the response of CNS sarcoidosis to adalimumab, cases of neurosarcoidosis isolated to the PNS were excluded. Patients were excluded if adalimumab was prescribed primarily for managing systemic manifestations. Patients were excluded if they did not have continued institutional follow-up after commencing adalimumab.

Data collection

Each patient's chart was reviewed for the purpose of gathering information on demographics, the clinical history of systemic and neurologic sarcoidosis, serum and cerebrospinal (CSF) laboratory values, pathology findings, treatment regimens, and outcomes. Magnetic resonance imaging (MRI) examinations were personally reviewed by the authors. In conjunction with the MRI review, neurology and rheumatology clinic notes were the primary means used to determine if relapses occurred while patients were on adalimumab.

Statistical analysis

Statistical analysis was conducted using Microsoft Excel™. Continuous variables were reported as medians and ranges while categorical values were expressed using fractions and percentages. In addition to variables being presented in aggregate form as a cohort, individual case data is also presented in tabular form to facilitate inspection of variables related to a particular case.

Literature review

On April 7th, 2021, we searched the PubMed database for cases of neurosarcoidosis treated with adalimumab by using the following search terms without date range or language restrictions: "adalimumab and neurosarcoidosis," "adalimumab and neurologic sarcoidosis," "adalimumab and sarcoidosis and central nervous system," "TNF alpha inhibitors and neurosarcoidosis," "TNF alpha inhibitors and neurologic sarcoidosis," "tumor necrosis factor alpha inhibitors and neurosarcoidosis," and "tumor necrosis factor alpha inhibitors and neurologic sarcoidosis."

Results

Results are presented for the current case series first followed by additional information gathered from the literature review noted at the end of the results section. Important findings are summarized in Table 1.

Patient characteristics and neurosarcoidosis phenotypes

The RPDR query yielded 652 possible patients, of which only 12 were exposed to adalimumab. Seven patients were included for review. Five patients were excluded: three had isolated PNS involvement, one possible case had equally competitive alternative diagnoses, and one probable case was lost to follow-up immediately after adalimumab was prescribed.

Patient characteristics are summarized in Table 2. Median age of neurosarcoidosis onset was 49 years (range 42–59). Four of seven patients were male. Patients were Caucasian (five), Middle Eastern (one), and African-Caribbean (one). With the exception of one patient, all others had pathologically proven sarcoidosis from mediastinal or hilar lymph node biopsy (meeting probable neurosarcoidosis diagnostic criteria) [10]. Neural histopathology was not obtained in any of the cases. One case met possible diagnostic criteria in the absence of pathology as the patient's pituitary gland and stalk involvement was classic for neurosarcoidosis with typical extra-neural manifestations (erythema nodosum, arthritis, and uveitis). Neurologic involvement was either concurrent with (four cases) or following (three cases) the systemic manifestations of sarcoidosis.

Neurologic phenotypes were predominantly central and included involvement of the spinal cord (four), cerebral parenchyma (one), pituitary (one), and leptomeninges (one). The cauda equina was involved in two cases. The median duration of neurosarcoidosis at the time of adalimumab initiation was 23 months (range 1–46). Patients experienced a median of two neurosarcoidosis attacks prior to initiation of adalimumab (range 1–3 attacks).

Treatment history, including prior infliximab use, and indications for adalimumab initiation

Adalimumab was not the first treatment choice for any patient in the cohort but was commonly a second line (four cases) or third-line (three cases) agent. Preceding treatments are noted in Table 1. Infliximab was used in three cases prior to adalimumab initiation. In two of those cases, neutralizing antibodies against infliximab developed, which resulted in disease relapse. Infliximab was ineffective in the third case. Three cases were switched from methotrexate on account of adverse effects (nausea, gastrointestinal discomfort, alopecia), and in one of those cases, methotrexate failed to resolve persistent enhancement of a spinal intramedullary lesion. Adalimumab was started in one case for maintenance treatment after prednisone had already been tapered from 80 mg daily to 10 mg daily.

Adalimumab dosing regimens, adverse effects, and concomitant immunosuppression

All patients were started on 40 mg every other week except for one patient who was started on weekly dosing for an active spinal cord relapse in the setting of neutralizing infliximab antibodies. One additional patient was eventually switched to weekly dosing after suffering a relapse on every other week dosing of adalimumab (case outlined in "Clinical and Radiographic Response"). Adalimumab was generally well tolerated in all but one case wherein recurrent infections eventually prompted adalimumab discontinuation. Therapeutic drug monitoring with serum adalimumab levels and anti-drug antibodies was not routinely performed in the MGB cases with the exception of one patient suffering a relapse as noted below in "Clinical and Radiographic Response."

Concomitant immunosuppression was utilized in four cases: three patients were taking methotrexate 25 mg weekly and one was treated with mycophenolate mofetil 1000 mg twice daily. Six patients were on prednisone at the time of adalimumab initiation. Compared with their starting doses of prednisone (10–80 mg daily), five of six patients were on lower doses at last follow-up (one case just starting adalimumab was on a stable dose of 10 mg daily). All patients in our cohort were on 10 mg or less of prednisone daily at last follow-up, including three who were on none.

Clinical and radiographic response

Aggregate patient outcomes are shown in Table 3. One patient suffered a clinical and radiographic relapse 13 months into adalimumab treatment. This patient had also recently started treatment with intravenous immunoglobulin (IVIG) and had suspended methotrexate treatment for the preceding 2 weeks on account of elevated liver enzyme levels. Though it is certainly possible that this attack represented a true relapse, it was postulated that holding methotrexate and concurrent use of IVIG may have contributed to breakthrough disease activity. Serum methotrexate level was undetectable at the time of the relapse. As a monoclonal antibody, adalimumab elimination may have been enhanced by IVIG; a serum adalimumab level was low and anti-adalimumab antibodies were absent. Of note, this patient remains on weekly adalimumab ten months later without

Table 1 Cases of neurosarcoidosis treated with adalimumab from the literature (first four cases) and the present case series (last seven patients)

Age/sex	Neurologic phenotype	Extraneural involvement	Biopsy	Prior Tx	Adalimumab SC dosing	AEs	Duration Tx, mos	Concur-rent IS	Pred dose	Response	Relapse	F/U, mos
22/F[8]	Meningitis	Eyes, lungs, LN	None	IVMP, P, MTX, HCQ	40 mg QOW	None	6	P, MTX	0	Improved	No	24
65/F[9]	Meningitis, CES	LN	Mediastinal LN	IVMP, P, MTX, IFX	40 mg QOW	None	Unk	Unk	Unk	Improved	No	Unk
58/M[9]	Meningitis	Lungs	None	P, MTX, IFX	40 mg QOW	HA	3	MTX	Unk	Stable/inactive	No	3
64/F[9]	Myelitis	LN	Inguinal LN	IVMP, P, MTX, IFX	40 mg QOW	None	18	None	0	Improved	No	18
49/M	Myelitis, Conus	LN	Hilar LN	MMF, IFX	40 mg QOW to > 40 mg QW	None	24	MTX	7	Improved	Yes	25
59/F	Myelitis	Lungs, LN	Mediastinal LN	P, MTX	40 mg QOW	None	29	None	0	Stable/inactive	No	27
42/M	Myelitis, Conus, CES	LN, Eye	Mediastinal LN	MMF, IFX	40 mg QW	None	18	MMF	0	Improved	No	19
55/F	Meningitis, CES	Cardiac, LN	Mediastinal LN	P, IFX, MMF	40 mg QOW	Infxn	11	P, MTX	4	Stable/active	No	12
49/M	Cerebral Parenchymal	LN	Mediastinal LN	P	40 mg QOW	None	5	P	10	Stable/inactive	No	4
49/M	Myelitis	Lungs, LN	Mediastinal & Hilar LNs	P, MTX	40 mg QOW	None	0	P, MTX	10	Stable/pending	No	1
43/F	Pituitary	Eyes, Skin, Joints	None	HCQ, MTX	40 mg QOW	Fatigue	9	None	0	Stable/active	No	10

All treatment-related variables pertain specifically to the patient's course at the time of or following initiation of adalimumab. Prednisone dosing is in milligrams (mg) and refers to the final prednisone dose at last follow-up

AEs adverse effects, *CES* cauda equina syndrome, *F/U* months of follow-up after initiation of adalimumab, *HA* headache, *IFX* infliximab, *Infxn* infection, *IS* immunosuppressant, *IVMP* intravenous methylprednisolone, *LN* lymph node, *MMF* mycophenolate mofetil, *MTX* methotrexate, *P* prednisone, *QOW* every other week, *SC* subcutaneous, *Tx* treatment, *Unk* unknown

Table 2 Patient characteristics of the Mass General Brigham (MGB) cohort and those reported in the literature

	Total	MGB cohort	Literature review
Cases	11	7	4
Age, yrs	49 (22–65)	49 (42–59)	61 (22–65)
Sex			
Male	5 (45%)	4 (58%)	1 (25%)
Female	6 (55%)	3 (42%)	3 (75%)
Race			
Caucasian	5 (45%)	5 (72%)	0 (0%)
Middle Eastern	1 (9%)	1 (14%)	0 (0%)
African-Caribbean	1 (9%)	1 (14%)	0 (0%)
Not reported	4 (36%)	0 (0%)	4 (100%)
Classification			
Probable NS	8 (73%)	6 (86%)	2 (50%)
Possible NS	3 (27%)	1 (14%)	2 (50%)
NS details			
Duration at adalimumab, mos	15 (1–46)	23 (1–46)	10 (3.5–27)
Attacks pre-adalimumab	2 (1–3)	2 (1–3)	2.5 (1–3)
CNS phenotypes			
Myelitis	5 (45%)	4 (58%)	1 (25%)
Cerebral	1 (9%)	1 (14%)	0 (0%)
Pituitary	1 (9%)	1 (14%)	0 (0%)
Meningitis	4 (36%)	1 (14%)	3 (75%)
Adalimumab use			
First line	1 (9%)	0 (0%)	1 (25%)
Second line	6 (55%)	4 (58%)	2 (50%)
Third line	4 (36%)	3 (42%)	1 (25%)
Final adalimumab dosing			
40 mg QOW	9 (82%)	5 (72%)	4 (100%)
40 mg QW	2 (18%)	2 (28%)	0 (0%)
Follow-up, mos	15 (1–27)	12 (1–27)	18 (3–24)
Lost/not reported	1 (9%)	0 (0%)	1 (25%)

Continuous variables are expressed as ranges and medians and categorical variables as fractions and percentages. Percentages may not add up to a total of 100% on account of rounding

mos months, *NS* neurosarcoidosis, *yrs* years, *QOW* every other week, *QW* every week

Table 3 Disease activity of neurosarcoidosis while undergoing treatment with adalimumab observed in the Mass General Brigham (MGB) cohort and cases reported in the literature

	Total	MGB cohort	Literature review
Relapses	1/10 (10%)	1/6 (17%)	0/4 (0%)
Improvement	5/10 (50%)	2/6 (33%)	3/4 (75%)
Remission maintenance	3/10 (30%)	2/6 (33%)	1/4 (25%)
Stable active disease	2/10 (20%)	2/6 (33%)	0/4 (0%)
Adalimumab discontinuation	3/10 (30%)	2/6 (33%)	1/4 (25%)

Only the MGB patients with adequate follow-up were included in the analysis (one patient with pending clinical and radiographic follow-up evaluations excluded). The "Total" column reflects the summative experience of MGB cases with those reported in the literature

further relapse. No other patients suffered clinical relapses while on adalimumab. One other patient discontinued adalimumab after 9 months due to the neurologist's perception that it was ineffective in reducing the degree of pituitary stalk thickening. In this case, radiographic findings were stable but persistent; no clinical relapse or worsening occurred.

Radiographic response included improvement of active disease in two cases, stabilization of active disease in two

cases, and maintenance of remission in two cases. One patient had only recently started adalimumab without follow-up neuroimaging available. In one case in whom adalimumab was discontinued on account of recurrent infections, worsening of cauda equina enhancement was seen 6 months after it was stopped. An example of a radiographic response to adalimumab is shown in Fig. 1.

Follow-up

Median duration of clinical follow-up in the case series was 12 months (range 1–27 months). No patients were lost to follow-up.

Literature review

One case series and two case reports were discovered in our literature review, representing a total of four patients. To date, only two cases of pathologically proven sarcoidosis with neurologic involvement undergoing treatment with adalimumab have been described in the literature [9]. In both cases of probable neurosarcoidosis (mediastinal biopsy with meningitis, inguinal lymph node biopsy with myelitis), the patients were switched from infliximab to adalimumab because of infections after having already failed methotrexate [9]. They were treated with 40 mg subcutaneously (SC) every other week with good response [9]. One case

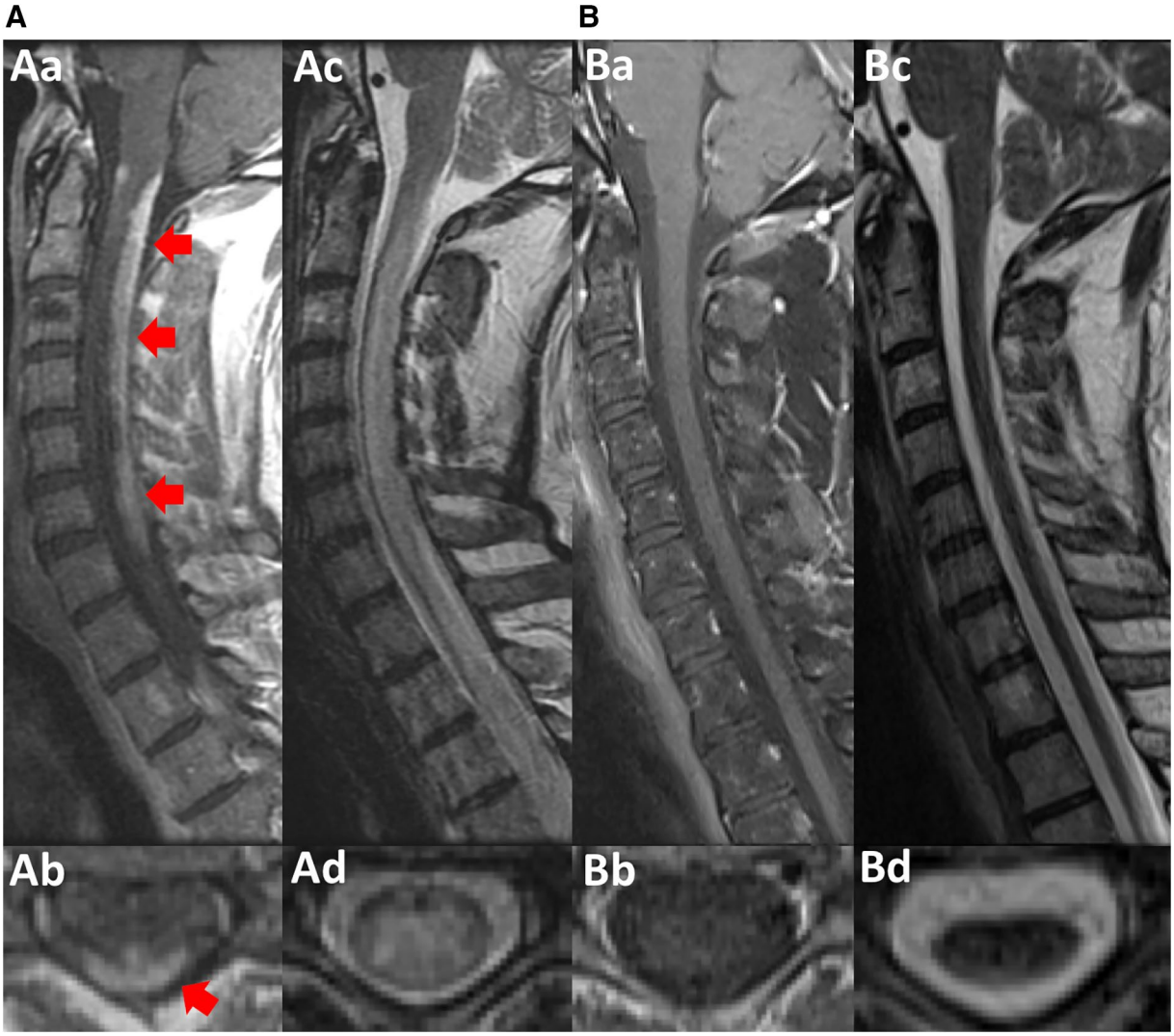

Fig. 1 Example of MRI response to adalimumab treatment. Pre-treatment (**A**) and post-treatment (**B**) MRI sequences from a case of myelitis from neurosarcoidosis. T1 weighted sequences with contrast are shown in Aa (sagittal) and Ab (axial), demonstrating longitudinal enhancement of the cervical spine predominantly in a dorsal subpial fashion (arrows). A "trident sign" can be seen in the axial plane of Ab (arrow) [26]. T2 weighted sequences are shown in Ac (sagittal) and Ad (axial), revealing a longitudinally extensive expansile T2 hyperintensity throughout the cervical spine. Following treatment with adalimumab at more frequent dosing, the enhancement (Ba and Bb) and T2 hyperintensity (Bc and Bd) had resolved

of possible neurosarcoidosis (hilar lymphadenopathy and lung disease with basilar meningitis having failed methotrexate and hydroxychloroquine) responded well to adalimumab 40 mg SC every other week [8]. Another case of possible neurosarcoidosis (lung disease with meningitis switched from infliximab due to headaches) was stable on adalimumab 40 mg SC every other week, but the drug was discontinued on account of recurrent headaches [8, 9]. One case of reported probable neurosarcoidosis was excluded because the MRI findings were not typical for sarcoidosis and did not correlate with the patient's reported symptoms [11].

Discussion

In this case series and literature review, we detail the experience of 11 patients with sarcoidosis of the CNS on adalimumab. These preliminary data suggest that adalimumab can be useful in the treatment of neurosarcoidosis and may represent a reasonable alternative to infliximab and other immunosuppressants when certain patient-specific factors prefer its use (logistical difficulties, patient preference for self-injections vs intravenous infusions, development of neutralizing antibodies on infliximab, or adverse effects). This limited dataset demonstrates efficacy in a variety of neurologic phenotypes—particularly meningeal disease and involvement of the spinal cord parenchyma.

Adalimumab was most often initiated after failure of or intolerance to more traditional agents: infliximab (three failures, three intolerances) and methotrexate (two failures, two intolerances). As a chimeric monoclonal antibody, infliximab is known to provoke anti-drug antibodies (ADA) that may neutralize its effect; two of our patients suffered disabling relapses of myelitis in the setting of anti-infliximab antibodies [12]. Adalimumab, a humanized monoclonal antibody, appears to have a lower risk for the development of ADA as outlined in a recent systematic review of this topic (54% with adalimumab vs 83% with infliximab) [12]. The presence of anti-infliximab antibodies has also been associated with a higher rate of infusion-related reactions than in those without them [12]. Adalimumab is also a costly medication that may be difficult to obtain insurance approval for, and we recognize that this factor may have affected the place of adalimumab in the hierarchy of medications trialed.

Only one of the 11 patients suffered a relapse while on adalimumab. In that particular case, the cause may have been multifactorial as described. Furthermore, the patient recovered well clinically and radiographically on more frequent dosing of adalimumab by the time of the latest MRI 10 months later. Adalimumab was discontinued in three patients: one on account of recurrent infections, one for headaches, and another due to lack of MRI improvement (though findings were stable). Excluding the one patient with limited follow-up, the other six patients (60% of those with follow-up) were able to derive real-world benefit from its use in the forms of resolution of active disease, maintenance of disease remission, and reduction of concomitant prednisone dosing. These findings are especially interesting to note in light of the relative refractory nature of disease in this patient group (median of two attacks in our patient cohort, adalimumab commonly used as a second- or third-line agent, and adalimumab frequently used after infliximab failure).

The optimal adalimumab dosing regimen for neurosarcoidosis remains unclear, but observations in this combined case series and literature review suggest that both weekly and every other week dosing may be reasonable choices. In our series (excluding the literature review), every other week dosing was the typical starting regimen while weekly dosing was used only in scenarios of high risk for permanent disability (refractory spinal intramedullary neurosarcoidosis). No patients underwent loading as has been used in patients with other rheumatologic diseases [13–16]. While prednisone dosing was heavily reduced while on adalimumab in our cohort, concomitant immunosuppressants were used in four of seven patients (three methotrexate, one mycophenolate mofetil). As is the nature of real-world management of neurosarcoidosis, there was heterogeneity in concomitant immunosuppressant therapy, which confounds our interpretation. It should be noted, however, that both methotrexate and mycophenolate mofetil at moderate-to-high doses have previously been shown to be only modestly successful at best in the prevention of neurosarcoidosis relapses, and we would therefore assert that these were not the primary contributors to relapse prevention in this series [17]. In the series by Bitoun et al., relapse rates of neurosarcoidosis were 47% with median methotrexate doses of 20 mg weekly and 79% with median mycophenolate doses of 2 g daily [17].

Though data are lacking for the indication of neurosarcoidosis, therapeutic drug monitoring (TDM) to simultaneously evaluate serum adalimumab levels and ADA may be helpful in understanding the factors that lead to relapse or lack of clinical response. When used in other diseases without predominant CNS involvement, low serum adalimumab levels in the presence of ADA have been associated with relapse or a lack of clinical response [18–21]. Concomitant methotrexate (7.5–15 mg weekly) can be useful in reducing the risk of ADA formation to TNF inhibitors [22–25]. In the absence of ADA, low serum adalimumab levels are suggestive of subtherapeutic dosing and therefore consideration should be given to adjusting the dose or frequency of adalimumab administration [18]. Though ADA can form early against adalimumab, therapeutic drug monitoring outside of the context of insufficient clinical response is of unclear utility at present in the treatment of neurosarcoidosis [19].

The small size of our patient cohort and the limited experience with adalimumab reported in the literature limit our ability to draw definitive conclusions about the efficacy of adalimumab for neurosarcoidosis. The study's retrospective design and incorporation of literature review contributed to non-standardized patient evaluation and management strategies but ultimately provided valuable insight into clinical scenarios that could prompt consideration of adalimumab. One patient with limited follow-up was included in this report for the purpose of discussing adalimumab treatment indications. The study would have additionally benefited from a longer period of follow-up.

A myriad of reasons might contribute to the paucity of reports on adalimumab use in neurosarcoidosis, including the drug's cost compared to more conventional agents and the lack of an FDA approval for this indication. Given the rarity of neurosarcoidosis and to address the possibility that negative experience with adalimumab is less likely to be reported in the literature, an important future direction will include comprehensively describing outcomes in a larger cohort of neurosarcoidosis patients derived from a multicenter collaborative effort.

Conclusion

Preliminary evidence in this case series and literature review suggests that adalimumab may be a reasonable therapeutic option for patients with neurosarcoidosis, including in those intolerant of or with disease refractory to commonly used agents (infliximab, methotrexate, and mycophenolate mofetil). Adalimumab, a usually well-tolerated agent, additionally provides certain benefits in terms of improved patient freedom and quality of life that are limited by other agents.

Author contributions SKH, MD: designed and conceptualized study; major role in the acquisition of data; analyzed the data; drafted the manuscript for intellectual content (Emory University School of Medicine, Atlanta). KK, MB BCH, MRCP: major role in the acquisition of data; revised the manuscript for intellectual content (Massachusetts General Hospital, Boston). JJC, MD: major role in the acquisition of data; revised the manuscript for intellectual content (Emory University School of Medicine, Atlanta). HR, MD: interpreted the data; revised the manuscript for intellectual content (Massachusetts General Hospital, Boston). NV, MD, MRCP-I, MRCP-UK: interpreted the data; revised the manuscript for intellectual content; study supervision (Massachusetts General Hospital, Boston).

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Declarations

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