



# Infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis

Manica Sodhi<sup>a</sup>, Karla Pearson<sup>a</sup>, Eric S. White<sup>b</sup>, Daniel A. Culver<sup>a,\*</sup>

<sup>a</sup> Respiratory Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA

<sup>b</sup> Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Michigan, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5360, USA

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## Summary

Central nervous system involvement is a severe manifestation of sarcoidosis that often requires aggressive immunosuppressive therapy. The most efficacious approach for refractory disease is unknown.

We reviewed the cases of four subjects who demonstrated active progression of neurosarcoidosis while under treatment with cyclophosphamide, and who were subsequently treated with infliximab.

All four subjects demonstrated rapid and substantial reversal of their clinical course. Radiologic findings were concordant with the clinical responses. There were no notable toxicities.

Treatment with infliximab may be more effective than cyclophosphamide for refractory central nervous system sarcoidosis. A larger, prospective study is warranted.

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Central nervous system (CNS) sarcoidosis, which occurs in up to 5% of individuals with sarcoidosis, confers substantial morbidity and may portend a poor prognosis.<sup>1,2</sup> Treatment of severe CNS sarcoidosis typically requires aggressive immunosuppression. Corticosteroids are the mainstay of

treatment, but there are patients whose disease continues to progress despite therapy with corticosteroids and immunosuppressants.

Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), a key mediator of sarcoidosis, has been tied to clinical course of the disease and is a prerequisite for granuloma formation.<sup>3,4</sup> Infliximab is a chimeric monoclonal antibody that blocks TNF- $\alpha$  bioactivity. *In vitro* data suggest that it can also lyse TNF- $\alpha$  producing cells, alter cytokine release and induce apoptosis.<sup>5,6</sup> There have been several observational reports of beneficial response to infliximab for refractory systemic sarcoidosis,<sup>7,8</sup> including CNS sarcoidosis.<sup>9</sup> However, the relative effectiveness of infliximab compared to conventional cytotoxic therapy has not been studied.

*Abbreviations:* Azathioprine, AZA; Central nervous system, CNS; Corticosteroids, CS; Magnetic resonance imaging, MRI; Methotrexate, MTX; Tumor necrosis factor  $\alpha$ , TNF- $\alpha$ .

\* Corresponding author. Tel.: +1 216 444 6508; fax: +1 216 445 8160.

*E-mail addresses:* [sodhim@ccf.org](mailto:sodhim@ccf.org) (M. Sodhi), [pearsok@ccf.org](mailto:pearsok@ccf.org) (K. Pearson), [docew@umich.edu](mailto:docew@umich.edu) (E.S. White), [culverd@ccf.org](mailto:culverd@ccf.org) (D.A. Culver).

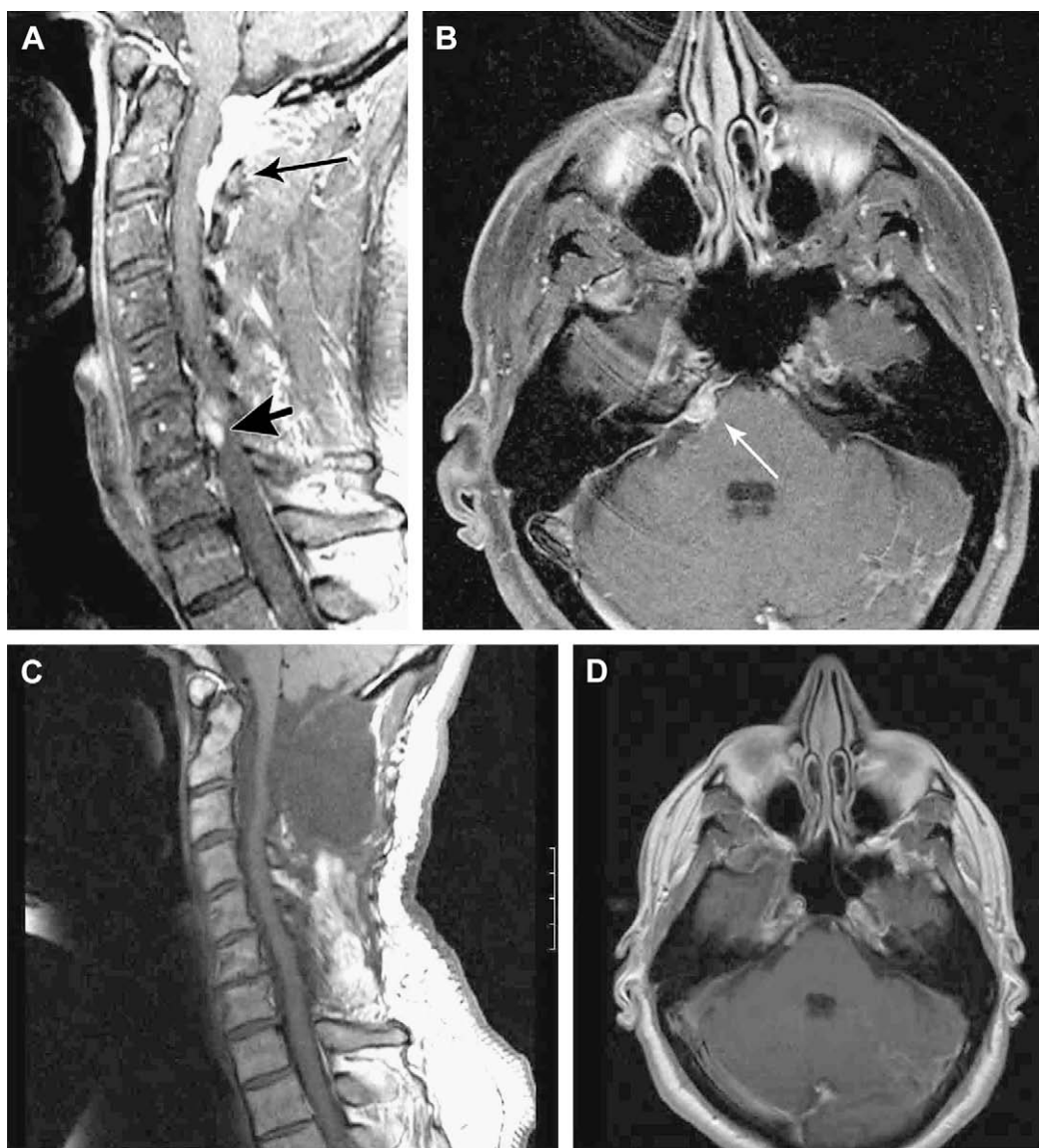
We recently observed dramatic responses to infliximab in four individuals with severe neurosarcoidosis that was refractory to treatment with steroids and cyclophosphamide. These examples afford an opportunity to indirectly assess the role of infliximab in severe neurosarcoidosis.

### Patient 1

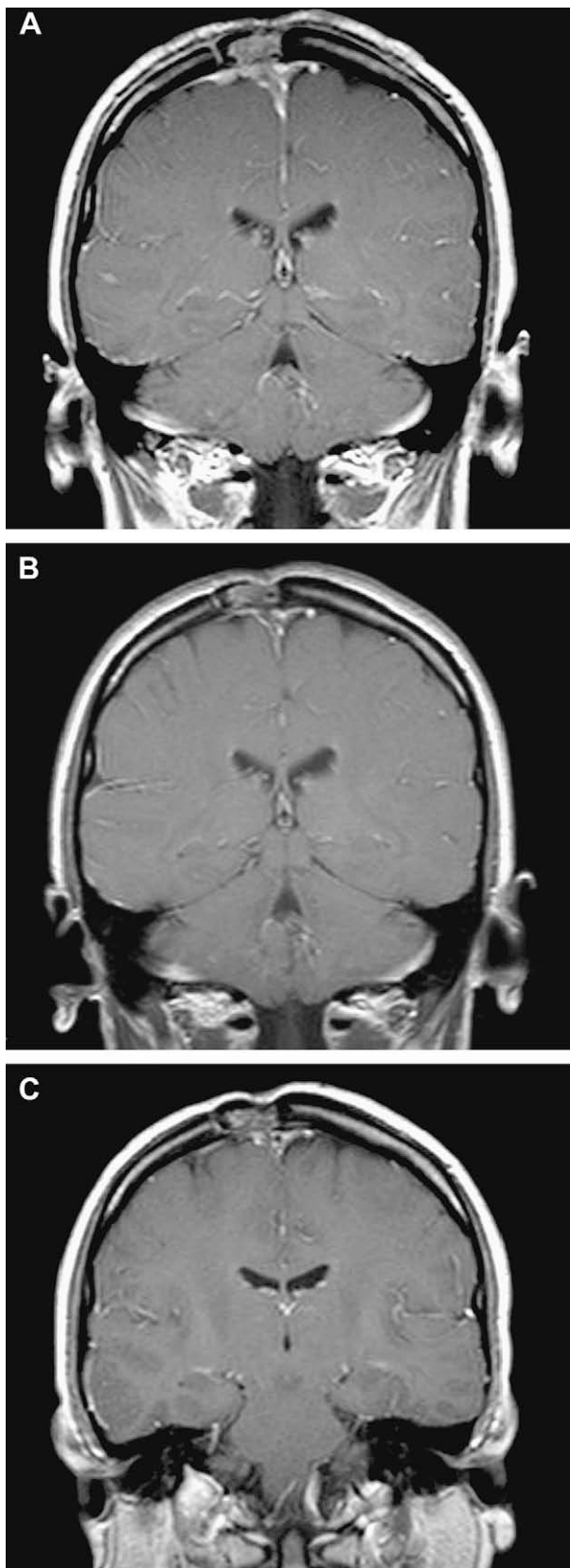
A 50-year-old Caucasian male presented with stiffness of the neck and shoulder girdle muscles, and left arm weakness. Magnetic resonance imaging (MRI) revealed a large enhancing lesion abutting the cervical spinal cord and multiple smaller lesions along the lower cervical spinal cord

(Fig. 1). The dominant mass-like lesion was resected via a suboccipital craniotomy, along with C1–3 and C6–7 laminectomies. Intraoperative findings included intradural and extradural masses with extension into the cerebellar fossa. Pathologic exam revealed multiple necrotizing and non-necrotizing granulomas associated with chronic inflammation. Special stains and cultures for acid-fast bacilli and fungi were negative. The diagnosis of sarcoidosis was substantiated when chest imaging revealed subcarinal lymphadenopathy, leading to a confirmatory transbronchial needle aspirate diagnosis.

After four weeks of treatment with prednisone at 60 mg/day, no improvement was noted either symptomatically or on MRI. Intravenous cyclophosphamide was added at this



**Figure 1** MRI findings for patient #1. Gadolinium-enhanced T1-weighted sagittal view (1A) demonstrated a large enhancing mass encroaching on the upper cervical spinal cord (arrow), with extension through the foramen magnum. There were also enhancing lesions in the lower cervical cord (arrowhead). Intraoperative findings revealed infiltration into the spinal cord and the nerve roots. Fig. 1B shows a transverse T1-weighted post-contrast image that revealed an enhancing lesion in the right cerebellopontine angle (arrow), with mild impingement on the pons and the right seventh and eighth cranial nerve root entry zone. Panels C and D demonstrate the MRI findings after treatment with infliximab.



stage, using a well-validated dosing regimen given every three weeks.<sup>10</sup> After six infusions (7.25 g total), there was no symptomatic improvement, but diplopia and blurred vision occurred, suggesting disease progression. A repeat MRI (Fig. 1B) revealed new nodular thickening and enhancement of the dura, as well as new intraparenchymal changes suspicious for granulomatous involvement. Treatment with high dose pulse intravenous solumedrol (1000 mg/day for three days) resolved the diplopia but the blurred vision persisted. At that point, the patient was switched to infliximab (5 mg/kg) and methotrexate. By the fourth infusion, there was complete resolution of the blurred vision along with notable improvement in the left upper extremity strength. An MRI obtained at that time revealed resolution of the radiographic abnormalities in the right cerebellopontine angle as well as of all the other enhancing lesions in the brain and spinal cord (Fig. 1C and D).

Currently, the patient has received a total of 13 infliximab infusions. He has been completely weaned off prednisone and has only modest left hand weakness remaining.

## Patient 2

A 36-year-old Caucasian female with longstanding headaches had an MRI that revealed a parasagittal mass at the posterior aspect of the right frontal lobe. Diagnostic biopsy via craniotomy demonstrated non-caseating granulomas consistent with sarcoidosis. Besides headaches, the patient had noted progressive symptoms of impaired short-term memory, intermittent dyspraxia, and episodes of confusion and vertigo. She received oral dexamethasone 8 mg three times daily for a period of six weeks with no improvement. Oral methotrexate 15 mg weekly was added; however, the symptoms continued to progress and she developed bilateral facial and lower extremity paresthesias. A repeat MRI (Fig. 2A) revealed much more prominent dural enhancement and soft tissue thickening at the right parietal vertex. In response, her therapy was switched to IV cyclophosphamide infusions and prednisone 5–80 mg/day. Five months later, she had not improved, and her course was complicated by spontaneous cranial incision dehiscence requiring operative repair. Cultures from the inflammatory tissue discovered intraoperatively were negative, but biopsies were not repeated.

Due to the lack of response to steroids and cyclophosphamide, infliximab (5 mg/kg) and oral methotrexate were started. By the second infusion, the patient began to notice improvement in the facial paresthesias. Her episodes of confusion decreased and her speech started to improve. Prednisone was gradually tapered to 5 mg daily. An MRI

**Figure 2** MRI findings for patient #2. A T1-weighted coronal section from patient 2 shows dural enhancement and thickening over the right parietal convexity (2A). This enhancement also extended further anteriorly and inferiorly along the falx. After the fourth infliximab infusion, there was a marked decrease in the extent of the dural enhancement (2B), which showed further improvement by the ninth infusion (2C).

(Fig. 2B) done after her fourth infusion showed a marked improvement in the dural enhancement. Except for some residual headaches, her neurologic symptoms entirely resolved.

To date, she has received a total of 13 infliximab infusions without any adverse events, with a sustained improvement in neurological symptoms. Attempts to decrease the frequency of her infliximab infusions to every six weeks led to recurrence of facial paresthesias. These again abated when the infusion frequency was increased to every four weeks. Prednisone continues at 5 mg daily. The most recent MRI shows complete resolution of all prior enhancing lesions.

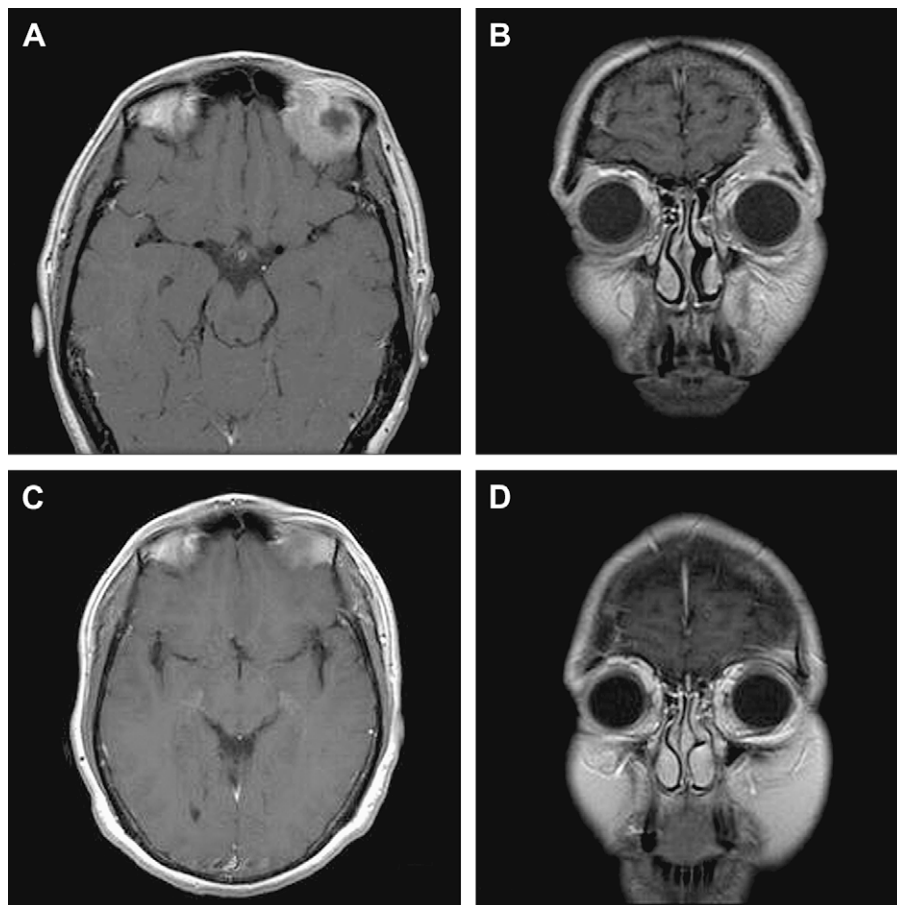
### Patient 3

A 49-year-old female developed flashes, blurry vision, and progressive color blindness in the right eye in 2002. She also complained of new dyspnea on exertion and cough, but these were not further assessed at that time. Her exam and imaging were consistent with bilateral optic neuritis; she was treated with empiric prednisone (up to 80 mg daily) and methotrexate 10 mg weekly. Mild left optic neuritis developed over the following two years, which precipitated

a consult in our institution. Her visual acuity at that time was 20/30 in the left eye and she had no light perception in the right eye. An MRI showed bilateral optic neuritis. A right optic nerve decompression was performed but the biopsy of the optic nerve sheath was non-specific. A diagnosis of probable CNS sarcoidosis was made on the basis of bronchoalveolar lavage lymphocytosis (23% lymphocytes), nodular infiltrates on the chest CT scan, negative stains and cultures, and a consistent neuroradiologic picture. Her therapy was changed to intravenous cyclophosphamide, along with prednisone (20 mg/day). Over the ensuing eight months, the left eye visual field defects progressed and her acuity also decreased to 20/50. MRI again showed evidence of bilateral optic neuritis.

The patient developed suicidal ideation due to her medical condition. The worsening of patient symptoms while on cyclophosphamide and prednisone prompted a switch to infliximab and methotrexate. By the second infusion, she noted a marked improvement in her vision. After the fourth infusion, the exam revealed left visual acuity of 20/20 and reversal of the visual field defects. A follow-up MRI showed resolution of the optic nerve enhancement.

She currently has received 16 infliximab infusions and her prednisone has been tapered to 10 mg/day. Her vision is stable and she reports no new neurological symptoms.



**Figure 3** MRI findings for patient #4. Contrast-enhanced transverse (3A) and coronal (3B) MRI images demonstrated a large mass extending through the orbital roof into the left frontal lobe. There was associated left eye proptosis. Follow-up imaging (3C and D) after the fourth infusion showed almost complete resolution of the orbital mass.

## Patient 4

A 49-year-old Caucasian woman with an 18-month history of trigeminal neuralgia developed worsening pain and paresthesias in her left vertex descending down to her left orbit. Physical exam revealed left eye proptosis and decreased visual acuity. An MRI (Fig. 3A and B) showed a large left orbital mass, extending through the orbital roof. Biopsy of the mass revealed non-necrotizing granulomas consistent with sarcoidosis, and all intraoperative cultures were negative. A chest X-ray revealed bilateral hilar lymphadenopathy, and confirmatory left cervical lymph node aspirate also suggested sarcoidosis. Over the ensuing months, she was treated with corticosteroids, methotrexate and oral cyclophosphamide (100 mg daily, total dose 13.2 g), all without clinical benefit. She was then started on infliximab infusions (3 mg/kg), with a notable improvement in paresthesias. A follow-up MRI performed after the fourth infusion showed almost complete resolution of the orbital mass (Fig. 3C and D). Mycophenolate 1000 mg BID was begun prior to the fifth dose of infliximab and complete resolution

of the mass was noted following the eighth infusion of infliximab. She is maintained only on mycophenolate mofetil currently and has had no recurrence of her mass.

## Summary

There are no randomized controlled studies focusing on CNS sarcoidosis on which to base treatment guidelines. Most patients with significant central nervous system sarcoidosis will exhibit a difficult course, and treatment is recommended unless there is only isolated facial nerve palsy or minimally symptomatic aseptic meningitis.<sup>11</sup> Prolonged courses of corticosteroids have been used most frequently; some authors have suggested use of prednisone doses up to 1 mg/kg,<sup>11</sup> although there are no controlled data to support this recommendation. However, most series have found that corticosteroid monotherapy is adequate in less than half of patients.<sup>12,13</sup> A range of alternatives have been used in this setting, including methotrexate, azathioprine, cyclophosphamide, cyclosporine, antimalarial agents, and

**Table 1** Clinical features of the reported patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Manifestations	Intra- and extradural cervical mass Left arm paresis and leg weakness Neck pain/stiffness	Meningitis Headaches Paresthesias Cognitive impairment	Bilateral optic neuritis Complete unilateral visual loss	Trigeminal neuralgia Facial pain/paresthesias Visual complaints
Disease duration	10 Months	2.5 Years	3 Years	2.5 Years
Therapies prior to CYC	CS	CS MTX	CS MTX	CS MTX, AZA
Prednisone dose (mg/day)	10–60	5–80	20–60	5–40
Total CYC prior to disease progression	7.25 g (IV) Seven infusions	6.5 g (IV) Seven infusions	13.5 g (IV) 12 Infusions	12 g (oral) 100 mg/day over four months
Evidence of disease progression on CYC	Sudden onset of severe diplopia and blurred vision Fatigue	Cranial wound dehiscence Progressing headaches and paresthesias MRI progression	Inexorable decline in visual acuity Concern for chiasmatic involvement on exam	Progressive paresthesias and visual complaints
Clinical response on infliximab	Continued paresis Diplopia resolved after IV solumedrol	Paresthesias resolved after #4 infusion HA dramatically better	L vision stabilized at 20/50 and visual field normalized after #1 infusion L vision 20/20 after #3 infusion	Near resolution of orbital mass on MRI after fourth infusion
Response evident (infusion #)	4	4	1	4
Other treatment	MTX + pred	MTX (elevation LFTs) leflunomide + pred	MTX + pred	Pred + MTX (tolerance) → MMF
Steroids weaned? (current dose)	Off	Yes (5 mg)	Yes (10 mg)	Off

radiation therapy. Small series suggest that cyclophosphamide may be the most effective of these<sup>10,13</sup>; cyclosporine and chlorambucil are rarely used in the modern era.

The four patients reported here developed varying manifestations of progressive CNS sarcoidosis that was refractory to high dose steroids and standard cytotoxic therapy. Not only did the patients fail to respond well to a cyclophosphamide-based regimen previously shown to be effective for CNS sarcoidosis,<sup>10</sup> but also they actually developed disease progression (Table 1).

All four patients responded to infliximab with dramatic improvements in their neurological symptoms. Response was evident early in the course of infliximab treatment, with marked symptomatic improvement noted as early as the second infusion in two patients and after the fourth infusion in the other two patients. Radiologic follow-up exams confirmed the clinical impressions. These effects were probably not due to methotrexate, which generally requires several months to effect significant change. Our experience extends the prior literature by demonstrating clinical superiority in a group of patients for infliximab compared with the standard therapy for CNS sarcoidosis.

No serious infections or adverse events were noted in any of our four patients. A potential concern relates to post-marketing data associating exposure to TNF antagonists with the new onset of demyelinating disorders.<sup>14,15</sup> These cases have been mainly described in patients treated with the soluble receptor antagonist, etanercept.<sup>14</sup> It is unclear, however, whether the incidence of new demyelination is any higher than expected background rates.<sup>15</sup> Any new neurologic symptom in patients treated with TNF antagonists requires careful investigation with this possibility in mind.

Our observations are consistent with the few prior case reports and small case series of the beneficial effects of infliximab therapy in patients with refractory systemic and CNS sarcoidosis. Although most of the patients in the case reports with CNS sarcoidosis described to have a positive response to infliximab had visual symptoms and primarily ocular inflammation, two of our patients had manifestations other than ocular involvement and still experienced dramatic benefit with infliximab. The fact that these patients were actively progressing while on cytotoxic therapy suggests that infliximab may be more efficacious than cyclophosphamide for CNS sarcoidosis. The largest reported experience with infliximab, a multicenter randomized, placebo-controlled trial of 138 patients with chronic sarcoidosis, included nine subjects with CNS sarcoidosis.<sup>16,17</sup> In general, physician assessment of the treatment effect for these nine patients was modest.<sup>17</sup> Possible explanations for the differences between these data and our observations include the less aggressive dosing regimen used in the trial, longer duration of disease (mean 7 years) in the trial subjects, and other baseline patient clinical features that were not assessed in the trial. Prospective controlled studies would be helpful to clarify the differential benefit of TNF antagonists in CNS sarcoidosis.

## Conflict of interest statement

The authors have no conflicts of interest to disclose.

## References

1. Burns TM. Neurosarcoidosis. *Arch Neurol* 2003;**60**(8):1166–8.
2. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. *Arch Neurol* 1985;**42**(9):909–17.
3. Marino MW, Dunn A, Grail D, Inglese M, Noguchi Y, Richards E, et al. Characterization of tumor necrosis factor-deficient mice. *Proc Natl Acad Sci U S A* 1997;**94**(15):8093–8.
4. Ziegenhagen MW, Benner UK, Zissel G, Zabel P, Schlaak M, Muller-Quernheim J. Sarcoidosis: TNF-alpha release from alveolar macrophages and serum level of sIL-2R are prognostic markers. *Am J Respir Crit Care Med* 1997;**156**(5):1586–92.
5. Scallon BJ, Moore MA, Trinh H, Knight DM, Ghayeb J. Chimeric anti-TNF-alpha monoclonal antibody cA2 binds recombinant transmembrane TNF-alpha and activates immune effector functions. *Cytokine* 1995;**7**(3):251–9.
6. Wong M, Ziring D, Korin Y, Desai S, Kim S, Lin J, et al. TNFalpha blockade in human diseases: mechanisms and future directions. *Clin Immunol* 2008;**126**(2):121–36.
7. Baughman RP, Lower EE. Infliximab for refractory sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2001;**18**(1):70–4.
8. Doty JD, Mazur JE, Judson MA. Treatment of sarcoidosis with infliximab. *Chest* 2005;**127**(3):1064–71.
9. Toth C, Martin L, Morrish W, Coutts S, Parney I. Dramatic MRI improvement with refractory neurosarcoidosis treated with infliximab. *Acta Neurol Scand* 2007;**116**(4):259–62.
10. Doty JD, Mazur JE, Judson MA. Treatment of corticosteroid-resistant neurosarcoidosis with a short-course cyclophosphamide regimen. *Chest* 2003;**124**(5):2023–6.
11. Hunninghake GW, Costabel U, Ando M, Baughman R, Cordier JF, du Bois R, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999;**16**(2):149–73.
12. Zajicek JP, Scolding NJ, Foster O, Rovaris M, Evanson J, Moseley IF, et al. Central nervous system sarcoidosis – diagnosis and management. *QJM* 1999;**92**(2):103–17.
13. Lower EE, Broderick JP, Brott TG, Baughman RP. Diagnosis and management of neurological sarcoidosis. *Arch Intern Med* 1997;**157**(16):1864–8.
14. Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, et al. Demyelination occurring during anti-tumor necrosis factor alpha therapy for inflammatory arthritides. *Arthritis Rheum* 2001;**44**(12):2862–9.
15. Magnano MD, Robinson WH, Genovese MC. Demyelination and inhibition of tumor necrosis factor (TNF). *Clin Exp Rheumatol* 2004;**22**(5 Suppl. 35):S134–40.
16. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du Bois R, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. *Am J Respir Crit Care Med* 2006;**174**(7):795–802.
17. Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS, et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. *Eur Respir J* 2008;**31**(6):1189–96.