Treatment of CNS sarcoidosis with infliximab and mycophenolate mofetil

Michael Moravan, BS
Benjamin M. Segal, MD

Address correspondence and reprint requests to Dr. Benjamin M. Segal, Dept. of Neurology, Holtom-Garrett Program in Neuroimmunology, University of Michigan, 4009 BSRB, 109 Zina Pitcher Place, SPC 2200, Ann Arbor, MI 48109-2200
bmsegal@umich.edu

ABSTRACT

Objective: To describe the effects of the anti-tumor necrosis factor neutralizing antibody, infliximab, and the antiproliferative immunosuppressant, mycophenolate mofetil, in refractory neurosarcoidosis.

Methods: We treated patients with biopsy-proven sarcoidosis and CNS involvement, who had failed treatment with steroids, with infliximab (5 mg/kg on weeks 0, 2, and 6, and then every 6–8 weeks thereafter). Six out of seven patients were co-treated with mycophenolate mofetil (1,000 mg PO BID). Patients underwent a review of symptoms and complete neurologic examination every 3 months and MRI scanning before and after 3–4 infusions of infliximab.

Results: All patients reported significant symptomatic improvement by the fourth infusion of infliximab, including relief of headache and neuropathic pain, reversal of motor, sensory, or coordination deficits, and control of seizure activity. Furthermore, infliximab therapy was universally associated with a decrease in lesion size or suppression of gadolinium enhancement as documented by MRI. A positive treatment response was attained irrespective of location or distribution of CNS involvement by sarcoidosis (dural/leptomeningeal based vs intraparenchymal; cord vs brain; single lesion vs multifocal). There were no serious adverse effects in a follow-up period spanning 6–18 months.

Conclusions: Combination treatment with mycophenolate mofetil and infliximab is a promising therapeutic approach for neurosarcoidosis. *Neurology*® 2009;72:337–340

GLOSSARY

A = azathioprine; **AA** = African American; **Cy** = cyclophosphamide; **E** = etanercept; **EDSS** = Expanded Disability Status Scale; **MMF** = mycophenolate mofetil; **MMSE** = Mini-Mental State Examination; **N** = neurologic; **O** = ophthalmologic; **P** = pulmonary; **Pq** = Plaquenil; **R** = rheumatologic; **Si** = sinuses; **S** = steroids; **TNF** = tumor necrosis factor; **VPS** = ventriculo-peritoneal shunt; **W** = white.

CNS infiltration occurs in approximately 5% of patients with sarcoidosis; it is associated with a less favorable course and accounts for a disproportionate amount of disability.¹ Neurosarcoidosis is often difficult to manage. In one of the larger clinical series, over 70% of patients relapsed or progressed despite treatment with corticosteroids and oral immunosuppressant agents.² Since neurosarcoidosis tends to flare in the midst of prednisone tapers, those afflicted are often subject to the complications of chronic corticosteroid usage. Hence, there is a clear need for novel therapeutic strategies in this disorder.

It has been speculated that tumor necrosis factor (TNF) α neutralizing agents might be effective in sarcoidosis based on animal studies demonstrating a critical role of TNF α in granulomatous inflammation and an association between TNF α expression in alveolar macrophages and active pulmonary sarcoidosis.^{3,4} Infliximab is a chimeric monoclonal human-murine IgG antibody directed against TNF α approved for the treatment of rheumatoid

Supplemental data at
www.neurology.org

From the Department of Neurobiology and Anatomy (M.M.) and the Departments of Neurology, Microbiology, and Immunology and the Cancer Center (B.M.S.), University of Rochester School of Medicine and Dentistry, NY.

B.M.S. is supported by grants from NINDS (NS047687-01) and NIAID (U19 AI056390; Project 2) of the National Institutes of Health, and the National Multiple Sclerosis Society.

Disclosure: Dr. Segal has received honoraria and grant support from Centocor for lectures, consultation, and research activities unrelated to the subject of this manuscript. He has also served as a consultant for Biogen, Serono, and TEVA.

Table 1 Patient characteristics

Patient no./sex/age, y/race	Neuroanatomic localization	Neurologic symptoms	Extra-CNS involvement	Initial symptoms*/duration, mo
1/F/53/AA	Extradural	Trigeminal neuralgia; facial numbness (V1-2)	O, Si, P, R	P/33
2/F/42/AA	Meningeal	Headache; complex partial seizures	R, Si	R/180
3/F/40/W	Intracerebral	Bifrontal headache	P	N/12
4/F/52/W	Meningeal	Global headache; facial diplegia	P, O	N/24
5/M/35/W	Intramedullary spinal cord	Lhermitte; numbness and paresthesias in hands/feet; urinary urgency	P	N/8
6/F/54/W	Intramedullary spinal cord	Spastic paraparesis; fatigue	P	N/72
7/F/52/W	Meningeal/intramedullary spinal cord	Ataxia; memory loss; urinary urgency	—	N/23

*Organ targeted during the presenting episode of sarcoidosis/length of time between clinical presentation of sarcoidosis and treatment with infliximab.

AA = African American; O = ophthalmologic; Si = sinuses; P = pulmonary; R = rheumatologic; W = white; N = neurologic.

arthritis, ankylosing spondylitis, psoriasis, and inflammatory bowel disease. In standard practice infliximab is administered in combination with oral immunosuppressant agents in order to prevent the development of human antichimeric antibodies (that can be associated with infusion reactions acutely and diminution of therapeutic efficacy chronically) as well as to capitalize on the synergistic effects of multimodal therapy.⁵ Mycophenolate mofetil (MMF), an antiproliferative drug, is increasingly used to treat immune-mediated disorders. Here we report the successful treatment of refractory neurosarcoidosis with infliximab and MMF.

METHODS **Subjects.** Patients were referred to the neurology outpatient clinic at Strong Memorial Hospital, Rochester, NY. Each patient had neurologic disease in the context of biopsy-proven sarcoidosis characterized by the presence of non-caseating granulomas in hilar or mediastinal lymph nodes (patients 2, 4, 5, 6), nasal mucosa (2), leptomeninges (7), an extradural mass (1), intramedullary lesions (6), or an intracerebral lesion (3). Cultures and stains of biopsied tissue were negative for mycobacterial or fungal infection.

Six of seven patients had pulmonary or hilar abnormalities demonstrated by CT scanning. None of the subjects had a concurrent inflammatory condition that might confound the diagnosis or a history or signs suggestive of lymphoproliferative disease or infections. Patients were screened for latent tuberculosis infection by purified protein derivative skin testing prior to institution of corticosteroids. All patients also had a chest X-ray shortly before starting infliximab.

Treatment. For primary therapy, patients were given corticosteroids in the form of IV methylprednisolone (1 g daily $\times$ 3 days) followed by a gradual prednisone taper (starting at 80 mg/

day with 10-mg decrements every 2 weeks). All of the patients flared during the midst of the taper, warranting additional measures.

Six of seven patients were started on MMF (500 mg twice daily) in combination with corticosteroids. The dose was increased to 1,000 mg BID over the next 4 weeks. Patients were given a 3-month trial of MMF or longer prior to initiation of infliximab, since the benefit of MMF therapy is usually evident in 2–3 months. Cell count, electrolytes, and liver function tests were monitored on a monthly basis during therapy.

Infliximab was administered by IV infusion at 5 mg/kg on weeks 0, 2, and 6 and then at 6- to 8-week intervals thereafter. Infusions were given over 2 hours at an outpatient center.

Monitoring and evaluation. Patients underwent a complete history and neurologic and physical examination at the time of diagnosis. Neurologic examinations and interval histories were obtained at 2- to 3-month intervals thereafter by the same examiner (B.M.S.).

MRI scans with gadolinium enhancement were performed using a 1.5 T magnet immediately before the first infusion of infliximab and following the third or fourth infusion.

RESULTS **Study population.** Patient characteristics are shown in table 1. The neurologic symptoms that brought patients 3, 4, 5, and 7 to our clinic were their presenting symptoms of sarcoidosis. Patients 3, 4, and 5 had asymptomatic pulmonary involvement detected by thoracic CT scanning; patient 7 had no evidence of organ involvement outside of the CNS. Surprisingly, none of the subjects had an elevated serum angiotensin converting enzyme level at the time of evaluation.

Patients were considered eligible for aggressive treatment due to the failure of conventional therapy to alleviate severe, debilitating headaches/neuralgia associated with a biopsy-proven granulomatous mass lesion (1, 3) or persistent meningeal enhancement

Figure MRI scans performed prior to institution of infliximab therapy (Pre-Tx) and after the third or fourth infusion (Post-Tx)

Postgadolinium T1-weighted images are shown. (A) Patient 3. An enhancing lesion in the occipital horn of the left lateral ventricle was reduced following infliximab infusions. (B) Patient 1. Axial (upper panels) and coronal (lower panels) views of an enhancing lesion in the left trigeminal cistern that extended through the foramen ovale and into the infratemporal fossa. The mass shrunk significantly by the fourth infusion. (C) Patient 2. Leptomeningeal/dural thickening and enhancement were reduced after treatment. (D) Patient 5. An enhancing intramedullary lesion receded after treatment.

and cranial neuropathies (4); refractory seizures or dementia and ataxia associated with meningeal enhancement and hydrocephalus (3, 7); and myelopathy associated with enhancing lesions in the spinal cord (5–7).

Response to corticosteroids and MMF. Each patient experienced a recrudescence of symptoms during the course of a prednisone taper, precluding a reduction in the dose below 50–20 mg daily. Six out of seven patients were started on MMF after 4–10 months of corticosteroid treatment failed to yield persistent remission. (Patient 5 elected not to go on oral immunosuppressant agents.) Although MMF resulted in symptomatic and radiologic stabilization, often at a reduced dose of prednisone, none of the patients could be completely weaned off corticosteroids after starting the immunosuppressant. The mean duration of MMF treatment prior to the introduction of infliximab was 8.5 months (with a range of 3–14 months).

Response to infliximab. Seven out of seven patients reported a dramatic improvement in symptomatology after 1–3 infusions of infliximab that was corroborated by MRI findings in every case (figure, table 2, table e-1 on the *Neurology*[®] Web site at www.neurology.org). Attempts to wean patient 1 after 31 months and patient 3 after 20 months of infliximab therapy resulted in recurrence of symptoms and MRI abnormalities. Both patients were restarted on infliximab with a positive response and remain on that treatment to the present time. The other five patients have consistently been treated with infliximab and MMF until the present (mean duration 31 months; range 24–39 months).

MMF and infliximab combination therapy was generally well tolerated with no incidents of leukopenia, liver dysfunction, or injection reactions. Patient 1 experienced transient fatigue immediately following the third infusion that did not recur thereafter. Patient 7 developed shingles after the second infusion, warranting a temporary discontinuation of infliximab/MMF for 2 months until the outbreak resolved. Otherwise there were no infections or other complications.

DISCUSSION The current study contributes to a growing body of literature that supports the use of infliximab in the treatment of sarcoidosis.^{6–9} We found that combination therapy with infliximab and MMF ameliorated CNS complications of sarcoidosis that had previously flared during a corticosteroid taper, irrespective of the site (cerebral hemispheres vs spinal cord; leptomeningeal vs extradural vs parenchymal) or distribution (solitary vs multifocal) of lesions. Patients universally experienced symptomatic improvement by the fourth infusion of infliximab that was sustained throughout a 24- to 39-month follow-up period. Although randomized studies will need to be conducted to assess the efficacy as well as the safety profile of our therapeutic regimen more

Table 2 Clinical response to infliximab			
Patient no.	Previous treatment/ concurrent treatment	Duration of treatment with steroids/MMF*/ infliximab (mo)	Response to infliximab
1	S, A/MMF	5/10/39	Alleviation of neuralgia (from 10/10 to 2/10 in intensity*); partial recovery of facial sensation
2	S/MMF	5/14/36	Resolution of headaches (from 5/10 to 0/10*); control of seizures
3	S/MMF	9/3/33	Alleviation of headaches (from 7/10 to 2/10 in intensity*); from daily to rare in frequency)
4	S, A/MMF	8/13/35	Resolution of headaches (from 8/10 to 0/10 in intensity*); partial recovery of facial movement and eye closure on left
5	S	5/-/26	Recovery of sensation; normalization of bladder and erectile function
6	S, Cy, E, Pq/MMF	10/7/24	Improvement in EDSS from 6.5 to 5; increase in energy level
7	S, VPS/MMF	4/4/28	Improvement in EDSS from 7 to 5.5; improvement in MMSE from 22 to 28

*Duration of treatment with MMF before addition of infliximab.

*Assessed using the visual analog scale.

MMF = mycophenolate mofetil; S = steroids; A = azathioprine; Cy = cyclophosphamide; E = etanercept; Pq = Plaquenil; EDSS = Expanded Disability Status Scale; VPS = ventriculo-peritoneal shunt; MMSE = Mini-Mental State Examination.

rigorously, our patients experienced relatively few side effects and no serious adverse events. None experienced infusion reactions or showed signs of resistance to infliximab therapy over time, perhaps due to suppression of human antichimeric antibodies by MMF. Of interest, one of our patients (6) did not respond to etanercept, but did respond to infliximab. Future studies are required to determine when and how to wean patients off infliximab and MMF once a satisfactory therapeutic response has been achieved. The suggestion that TNF inhibitors may be therapeutic in neurosarcoidosis should not be extrapolated

to all neuroinflammatory disorders. Indeed, TNF neutralizing agents have been found to exacerbate multiple sclerosis.¹⁰ Therefore, we recommend that this treatment regimen be restricted to patients with biopsy-proven sarcoidosis.

Received December 23, 2006. Accepted in final form October 15, 2008.

REFERENCES

1. Ferriby D, de Seze J, Stojkovic T, et al. Long-term follow-up of neurosarcoidosis. *Neurology* 2001;57:927–929.
2. Zajicek JP, Scolding NJ, Foster O, et al. Central nervous system sarcoidosis: diagnosis and management. *QJM* 1999;92:103–117.
3. Baughman RP, Strohofer SA, Buchsbaum J, Lower EE. Release of tumor necrosis factor by alveolar macrophages of patients with sarcoidosis. *J Lab Clin Med* 1990;115:36–42.
4. Kindler V, Sappino AP, Grau GE, Piguet PF, Vassalli P. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. *Cell* 1989;56:731–740.
5. Han PD, Cohen RD. Managing immunogenic responses to infliximab: treatment implications for patients with Crohn's disease. *Drugs* 2004;64:1767–1777.
6. Pritchard C, Nadarajah K. Tumor necrosis factor alpha inhibitor treatment for sarcoidosis refractory to conventional treatments: a report of five patients. *Ann Rheum Dis* 2004;63:318–320.
7. Carter JD, Valeriano J, Vasey FB, Bogner B. Refractory neurosarcoidosis: a dramatic response to infliximab. *Am J Med* 2004;117:277–279.
8. Pettersen JA, Zochodne DW, Bell RB, Martin L, Hill MD. Refractory neurosarcoidosis responding to infliximab. *Neurology* 2002;59:1660–1661.
9. Sollberger M, Fluri F, Baumann T, et al. Successful treatment of steroid-refractory neurosarcoidosis with infliximab. *J Neurol* 2004;251:760–761.
10. Sicotte NL, Voskuhl RR. Onset of multiple sclerosis associated with anti-TNF therapy. *Neurology* 2001;57:1885–1888.