

Treatment of Orbital Myositis with Adalimumab (Humira)

ALEXA B. ADAMS, MICHAEL KAZIM, and THOMAS J.A. LEHMAN

ABSTRACT. Adalimumab is a fully humanized IgG1 monoclonal antibody to tumor necrosis factor- α . We describe 2 patients (17 and 13 years of age) with refractory, steroid-dependent, recurrent nonspecific orbital myositis not controlled with standard immunosuppressive medications. Both improved with adalimumab treatment, allowing reduction in corticosteroid dosage without disease flare. (J Rheumatol 2005;32:1374–5)

Key Indexing Terms:

ADALIMUMAB

ORBITAL MYOSITIS

TUMOR NECROSIS FACTOR- α

Nonspecific orbital myositis is an inflammatory condition of unknown etiology. Presenting symptoms of orbital myositis include pain, orbital swelling, diplopia, nausea, and erythema¹. Infection, malignancy, and systemic illness must be excluded as potential etiologies¹. The acute inflammatory phase is characteristically corticosteroid-responsive; however, relapses may occur when the corticosteroid dose is lowered^{1,2}. While some patients experience only a single episode, orbital myositis is most often a chronic, recurrent condition. Many patients require repeated, prolonged treatment with steroids². The side effects of longterm corticosteroid usage (including premature atherosclerosis, osteoporosis, diabetes, growth retardation, and truncal obesity) add substantially to the morbidity of this condition. Intravenous immunoglobulin, cyclophosphamide, cyclosporine, methotrexate (MTX), and low-dose orbital radiation have been used as steroid-sparing agents, with varying degrees of success^{1,3,4}. Orbital radiotherapy has not generally been recommended in patients younger than 20 years of age due to the perceived risk of induced malignancy.

There is evidence to suggest a role for the anti-tumor necrosis factor- α (TNF- α) agents in treatment of inflammatory orbital disease. Recent case reports described successful treatment of idiopathic orbital inflammation with infliximab^{5,6}. Etanercept and infliximab have been well tolerated; however, they appear to be more effective in controlling the arthritis associated with uveitis than the intraocular inflam-

mation itself⁷. Foster, *et al* observed no significant efficacy compared to placebo when using etanercept to prevent relapses of uveitis in patients being tapered from methotrexate⁸. This study, however, was limited by a small sample size.

Adalimumab is a fully humanized IgG1 monoclonal antibody to TNF- α ⁹. There have been no published clinical trials to date of adalimumab for the treatment of nonspecific orbital myositis. We describe 2 patients (17 and 13 years of age) with refractory, steroid-dependent, recurrent nonspecific orbital myositis not controlled with standard immunosuppressive medications. Both improved with adalimumab treatment, allowing reduction in corticosteroid dosage without disease flare.

CASE REPORTS

Case 1. A 17-year-old woman presented with headache, right orbital swelling, pain, diplopia, and nausea. There was no fever or systemic symptom. Visual acuity at presentation was 20/20. Computerized tomography of the head and cerebrospinal fluid studies were normal, including protein, glucose, gram stain, bacterial culture, Lyme, VDRL, and Cryptococcus. Magnetic resonance imaging (MRI) revealed orbital myositis as evidenced by right medial rectus muscle enlargement and tendon enhancement. Laboratory studies including erythrocyte sedimentation rate (ESR), angiotensin-converting enzyme (ACE), creatinine phosphokinase (CPK), aldolase, antinuclear antibody (ANA), cytoplasmic anti-neutrophil antibodies (C-ANCA), peripheral (P)-ANCA, and thyroid function tests were normal. Chest radiograph was normal. Treatment with prednisone 80 mg po daily produced improvement. Nortriptyline and diclofenac were added for symptomatic control. Prednisone was tapered to 5 mg daily over 5 months. Two months later she experienced recurrent right eye pain consistent with recurrent disease. Her symptoms responded to prednisone 20 mg daily. Two months later she developed left eye pain, and MRI showed left lateral rectus myositis. Prednisone was increased from 20 to 70 mg daily and MTX was started at 15 mg po weekly. Biopsy of the left orbital fat and left lateral rectus muscle excluded existence of infection, malignancy, or vasculitis, and confirmed the diagnosis of nonspecific orbital myositis.

Prednisone was decreased to 15 mg daily over the ensuing 4 months. The disease recurred, and prednisone was increased to 40 mg daily. MTX was switched to subcutaneous administration (50 mg weekly) and prednisone gradually reduced to 15 mg daily. MTX was discontinued after 4 months because of a rash. Mycophenolate mofetil was started at 1 g twice daily, but her disease flared 4 weeks later. Prednisone was increased to 30 mg daily. Mycophenolate mofetil was discontinued because of elevated

From the Division of Pediatric Rheumatology, Hospital for Special Surgery; and Department of Ophthalmology, New York Presbyterian Hospital, Columbia Campus, New York, New York, USA.

A.B. Adams, MD, Fellow, Division of Pediatric Rheumatology, Hospital for Special Surgery; T.J.A. Lehman, MD, Chief, Division of Pediatric Rheumatology, Hospital for Special Surgery, Professor of Clinical Pediatrics, Weill Cornell Medical Center, New York, NY; M. Kazim, MD, Department of Ophthalmology, New York Presbyterian Hospital.

Address reprint requests to Dr. T.J.A. Lehman, Division of Pediatric Rheumatology, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021.

Accepted for publication February 3, 2005.

hepatic enzymes. Over the next 3 months, she received intravenous cyclophosphamide (750 mg/m²/mo). Between the second and third doses, the disease recurred despite treatment with 1 g intravenous solumedrol and 60 mg prednisone daily.

Adalimumab was started at a dose of 40 mg sq weekly after 2 years of recurrent disease. Prednisone has been tapered to 1 mg daily and all other drugs have been discontinued, with no recurrence of disease for more than one year.

Case 2. A 13-year-old girl presented with left eye swelling and pain. Visual acuity at presentation was 20/20. MRI showed enlargement of the left lateral rectus muscle with enhancement of the tendon. Nonspecific orbital myositis was diagnosed and prednisone 40 mg daily was begun. ESR, ANA, C-ANCA and P-ANCA, ACE, CPK, aldolase, and thyroid function tests were all normal or negative. Her symptoms resolved and prednisone was discontinued after 8 weeks. Five months later she experienced right eye pain. MRI showed enlargement of the right lateral rectus muscle with tendon enhancement. Prednisone 40 mg daily was started and increased to 80 mg when she complained of diplopia. Over the next year, the prednisone was slowly discontinued, without recurrence. Two years later she presented again with left eye pain. MRI showed orbital myositis, with enlargement and enhancement of the medial rectus muscle. Prednisone was restarted at 60 mg daily, and discontinued after 3 months. Two months later the orbital myositis recurred. Based upon the successful treatment of our first patient, adalimumab was started at 40 mg sq weekly. Prednisone has been decreased to 5 mg every other day, and she remains well 9 months later.

Both patients have recently been examined, and remain in remission.

DISCUSSION

Nonspecific orbital myositis is an inflammatory condition of unknown etiology. It may be a chronic, recurrent disease requiring prolonged use of corticosteroids. Orbital myositis may occur in association with other immune mediated conditions, suggesting that orbital myositis is autoimmune mediated rather than infectious¹. Prednisone, MTX, and intravenous immunoglobulin have been successful alone or in combination in some cases^{3,4}. Longterm use of oral corticosteroids is associated with undesirable side effects. MTX carries the risk of liver and bone marrow toxicity and pulmonary fibrosis; however, with close monitoring, severe side effects are rare.

Adalimumab is a fully humanized monoclonal antibody to human TNF- α administered as weekly or every other week subcutaneous injections. It interferes with the binding of TNF- α to cell-surface receptors blocking the normal inflammatory response⁹. TNF- α -blocking agents are being utilized with increasing frequency in the treatment of inflammatory disease. In our experience, adalimumab is more effective than either etanercept or infliximab for treatment of uveitis, prompting our selection of this agent in these cases. Both patients failed multiple courses of corticosteroids prior to initiation of adalimumab. The use of adalimumab in our patients produced prompt, long-lasting improvement and the ability to reduce corticosteroid doses to nontoxic levels. While it is possible that the response may have coincided with the natural course of an unpredictable disease, we believe the regular pattern of chronic recurrence was altered by the addition of adalimumab. We suggest adalimumab is a useful steroid-sparing agent for patients with nonspecific orbital myositis.

All TNF- α -blocking agents are known to increase the risk

of tuberculosis, necessitating screening for latent tuberculosis infection before treatment is initiated. As with any immunosuppressive agent, the risk of severe infection is increased. The risk of lymphoma appears to be elevated in patients receiving TNF- α -blocking agents, although these data come from patients with long-standing rheumatoid arthritis, who are known to be at increased risk for non-Hodgkin's lymphomas¹⁰. The significance of this risk remains to be confirmed, and in the meantime treating physicians should maintain a high degree of suspicion for medication associated malignancies¹¹. Rarely reported adverse events have included drug induced lupus, seizures, pancytopenias, and demyelinating disease¹¹. As with any new drug, patients taking adalimumab should be monitored for longterm side effects. Adalimumab has been used with increasing frequency in the pediatric population to treat refractory juvenile arthritis and it is our hope that it will be approved by the US Food and Drug Administration for use in children.

We suggest adalimumab is a valuable adjunct in the treatment of nonspecific orbital myositis. Large, controlled, prospective trials are desirable, but the infrequency of this condition makes it unlikely that true controlled trials will be accomplished.

REFERENCES

1. Yuen SJ, Rubin PA. Idiopathic orbital inflammation: ocular mechanisms and clinicopathology. *Ophthalmol Clin North Am* 2002;15:121-6.
2. Mombaerts I, Koornneef L. Current status in the treatment of orbital myositis. *Ophthalmology* 1997;104:402-8.
3. Smith JR, Rosenbaum JT. A role for methotrexate in the management of non-infectious orbital inflammatory disease. *Br J Ophthalmol* 2001;85:1220-4.
4. Nakatani-Enomoto S, Aizawa H, Koyama S, Haga T, Takahashi J, Kikuchi K. A patient of recurrent orbital myositis with good response to high-dose intravenous immunoglobulin therapy [Japanese]. *Rinsho Shinkeigaku* 2002;42:154-7.
5. Wilson MW, Shergy WJ, Haik BG. Infliximab in the treatment of recalcitrant idiopathic orbital inflammation. *Ophthal Plast Reconstr Surg* 2004;20:381-3.
6. Garrity JA, Coleman AW, Matteson EL, Eggenberger ER, Waitzman DM. Treatment of recalcitrant idiopathic orbital inflammation (chronic orbital myositis) with infliximab. *Am J Ophthalmol* 2004;138:925-30.
7. Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. *Arthritis Rheum* 2001;45:252-7.
8. Foster CS, Tufail F, Waheed NK, et al. Efficacy of etanercept in preventing relapse of uveitis controlled by methotrexate. *Arch Ophthalmol* 2003;121:437-40.
9. Van de Putte LBA, Rau R, Breedveld FC, et al. Efficacy and safety of the fully human anti-tumor necrosis factor-alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. *Ann Rheum Dis* 2003;62:1168-77.
10. Khanna D, McMahon M, Furst DE. Safety of tumour necrosis factor-alpha antagonists. *Drug Saf* 2004;27:307-24.
11. Brown SL, Greene MH, Gershon SK, Edwards ET, Braun MM. Tumor necrosis factor antagonist therapy and lymphoma development. Twenty-six cases reported to the Food and Drug Administration. *Arthritis Rheum* 2002;46:3151-8.