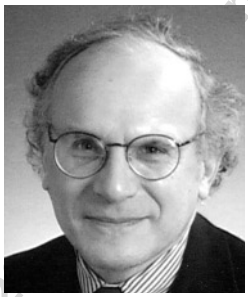
Editorial

Blind Insight: Eyeing Anti-Tumor Necrosis Factor Treatment in Uveitis Associated with Behçet's Disease



Many clinicians contend that the number of therapies promoted to treat a specific disease is directly proportional to the lack of success in treating that disease. If this dictum is true, ocular Behçet's disease (BD) must truly be refractory to therapy. Alkylators, azathioprine, methotrexate, antibiotics, dapsone, levamisole, cyclosporine, tacrolimus, colchicine, thalidomide, corticosteroids, pheresis, alpha-interferon (α-IFN), monoclonal antibody to either CD52 (Campath 1) or the interleukin 2 receptor (daclizumab), and intravenous immunoglobulin have each been assessed as treatment for this potentially devastating disease.

In this issue of *The Journal* Ohno and colleagues add another candidate to this list of interventions: infliximab[2]. Is there reason to believe that this modality is superior to its predecessors?

BD is a multisystem inflammatory disease with strong ethnic predilections. Although uncommon in North America, BD is endemic in parts of Southeast Asia and along the Silk Route through the Middle East. Its etiology is unknown, but genetic factors including a polymorphism in the TNF promoter region are increasingly being defined[1]. An infectious trigger is suspected but not proven. Intraocular inflammation, or uveitis, typifies BD, and it is often the dominant clinical finding. The ocular inflammatory disease is frequently characterized by bilaterality, intense and sudden recurrences, and retinal vasculitis.

In the studies described by Ohno and colleagues[2], 13 patients with active BD were treated for 14 weeks with repeated intravenous doses of infliximab at either 5 or 10 mg/kg. The frequency of ocular attacks was compared before and after treatment. Both dosages succeeded dramatically in reducing the rate of attacks. The series is consistent with other favorable reports about treating the uveitis associated with BD with a monoclonal antibody to tumor necrosis factor (TNF), including peer-reviewed publications from Greece[3], England[4], and Spain[5], as well as case reports[6] and abstracts[7,8]. In the largest series published to date[3], 24 of 25 patients with ocular BD experienced a prompt remission of the eye disease after a single infusion. In 15 of these patients infusions were repeated periodically for 32 weeks. Sixty percent of the patients receiving sustained therapy had no further attacks during therapy. A letter from Mansoor, however, calls attention to the likelihood of recurrent attacks from a strategy involving a single treatment[9].

Attempting to answer questions inevitably prompts more questions. What is the optimal dosage of infliximab therapy for BD? In the Ohno study, the lower dose was comparable to the higher dose, but the study size is inadequate to define ideal dosage. What is the optimal frequency of therapy? Since BD is episodic, should treatment be given only with each attack? Or will that approach promote synthesis of neutralizing antibodies, ultimately reducing efficacy while permitting some ocular damage during the inevitable delay until the drug has been delivered? Is it necessary or desirable to give infliximab with another immunosuppressive such as cyclosporine, methotrexate, or azathioprine? How does infliximab compare with other TNF inhibitors or other biologics such as α-IFN? Although the answer requires a direct test, one abstract reported that etanercept was not efficacious in treating BD[10] and another from The Netherlands reported success using infliximab in several patients who had been treated previously with α-IFN[8]. How effective is TNF inhibition for non-ocular manifestations of BD? Here the current report hints at benefit, but numbers of patients and details limit the value of that impression. Does a favorable experience in treating the uveitis of BD mean that TNF inhibition should be effective for other forms of uveitis, such as so-called idiopathic disease or that associated with Crohn's disease, ankylosing spondylitis, or sarcoidosis? While the response of each of these latter syndromes to TNF inhibitors is encouraging, uveitis is a heterogeneous collection of diseases. Just as a medication effective for rheumatoid arthritis might not be effective for rheumatoid vasculitis, so the extrapolation that a medication effective for colitis or arthritis will be efficacious for associated uveitis demands testing. And is TNF inhibition safe in

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treating BD? Here, too, while the report of Ohno, *et al* is encouraging despite one case of tuberculosis, the study size is too small to exclude the possibility of unique toxicities associated with this disease. The effect of TNF inhibition on infectious complications, on thrombosis, and on the neurological manifestations of BD especially deserves careful scrutiny. Some animal data indicate that TNF-α has an antithrombotic effect[11]. In our own open label study of infliximab therapy for various forms of uveitis, we have observed both pulmonary embolism and coronary artery thrombosis during the course of therapy[12]. Since BD itself is associated with thrombosis, TNF inhibition must be used very cautiously in patients with this predisposition.

What evidence is adequate to justify the use of infliximab for one's patients with uveitis associated with BD? The study by Ohno and colleagues obviously falls short of the gold standard, a randomized controlled trial (RCT). Even the RCT, however, will not be adequate in size to reassure a practitioner that TNF inhibition is unassociated with unique toxicities in patients with BD.

Historical controls are by definition imperfect but nonetheless informative. Untreated ocular BD frequently leads to blindness in less than 4 years from its onset[13]. In an RCT, Masuda and colleagues[14] studied cyclosporine at 10 mg/kg/day and concluded that this treatment was beneficial. In the second RCT, Yazici and colleagues[15] evaluated azathioprine at 2.5 mg/kg/day and noted benefit. Ozyazgan and colleagues randomized patients to intravenous cyclophosphamide versus cyclosporine at a dose of 5 mg/kg/day[16]. These investigators concluded that cyclosporine was superior to cyclophosphamide, but that improved visual acuity was not sustained after 24 months' followup. Improved acuity is an appropriate goal if treatment begins while the patient has active disease, but stable acuity is a more appropriate endpoint if the therapy begins while inflammation is in remission. Whitcup and colleagues noted stable or improved acuity in 28 of 37 eyes from 19 patients with a nearly 2-year followup when cyclosporine was combined with prednisone, but at dosages that most rheumatologists currently would try to avoid for chronic therapy[17]. The most optimistic report on therapeutic response is from Kotter, *et al*, who studied α-IFN in 50 patients with ocular BD and concluded that the response rate was 92%[18]. In a smaller study that did not focus on the ocular disease, O'Duffy and colleagues noted that 3 of 10 patients with BD discontinued α-IFN therapy due to toxicity[19]. In this study flu-like symptoms were universal, but seizure and psychosis were also reported. In the studies cited above, differing designs and differing endpoints make it very challenging to compare results to studies using infliximab.

For most practitioners there are different levels of proof applied to therapeutic decision-making. In an ideal world, the questions: (1) Is this a therapy that I would recommend for myself or a family member? (2) Is this a therapy that I would prescribe as a first choice for patients in my practice? or (3) Is this a therapy that insurers are willing to approve? should each have the same answer. The world is not ideal.

Sometimes I chide my students, residents, and fellows: "The trouble with medical education is that we learn from our mistakes." While I say this in jest, the fact is that our personal experience always profoundly affects our thinking even though our personal experience never achieves the rigor of a randomized controlled trial. I have personally treated 9 patients successfully with infliximab for BD: 5 patients as part of the above mentioned open label trial evaluating infliximab for uveitis, 2 patients with severe uveitis with the treatment supervised by a referring physician remote from my own practice, and 2 patients with predominantly non-ocular disease. My personal experience is consistent with Ohno, Sfikakis, and others. My personal experience with other therapies including α-IFN, alkylators, and the combination of cyclosporine with azathioprine has been much less successful.

I recognize that there is a huge bias to publish triumphant interventions and to be silent about attempts at treatment that fail. I recognize that my personal experience is laden with bias and observational error. I recommend caution in using a TNF inhibitor in a patient with central nervous system disease or a thrombotic diathesis. I recommend that ideally patients should be active participants in the choice of a therapeutic regimen. Clearly an RCT would be a welcome addition to our knowledge and a direct comparison with α-IFN would surely be informative. Even with these caveats in mind, my current belief is that infliximab is the drug of choice for ocular BD. The study by Ohno and colleagues in this issue strongly supports this conclusion.

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