UVEITIS

Possible New Treatment Models for Behçet Disease

BY ERIC BUTTERMAN, CORRESPONDENT

Olympic medalist Sanya Richards made public her struggle with Behçet disease a few years ago in hope of bringing more research attention to the multisystem, vascular inflammatory syndrome. That hope may be paying off, as new treatment models—interferon and inhibitors of tumor necrosis factor—appear to be winning over physicians caring for patients with Behçet.

Natural History

Usually diagnosed in the second or third decade of life, Behçet can cause vision-threatening uveitis, debilitating arthritis, terrible aphthous ulcers of the mouth and genitals, and, in some patients, brain lesions. It is most common in the Middle East and Asia, especially Turkey, Israel and Japan, and has a strong association with the major histocompatibility complex antigen HLA-B51. Up to 20,000 Americans have Behçet disease, although the American Behçet's Disease Association, for which Ms. Richards writes a blog, suggests that the prevalence may be higher than reported.

Relapsing, remitting. As is the case in many inflammatory syndromes, Behçet symptoms are episodic for many patients. Ilknur Tugal-Tutkun, MD, a professor of ophthalmology at Istanbul University, believes that emotional stress is a clear adverse factor for patients who relapse after a period without symptoms. She recalls countless examples of symptoms improving when the stressors were lifted. "I have seen many patients who went into spontaneous remission after getting divorced or after changing a stressful job and, conversely, patients in remission who developed severe exacerbations after losing a job or losing a loved one. And any stressful situation, such as tiring trips, sleepless nights, long hours at work, catching the flu and other infections can trigger attacks. I advise my patients to avoid these situations."

Diagnosis

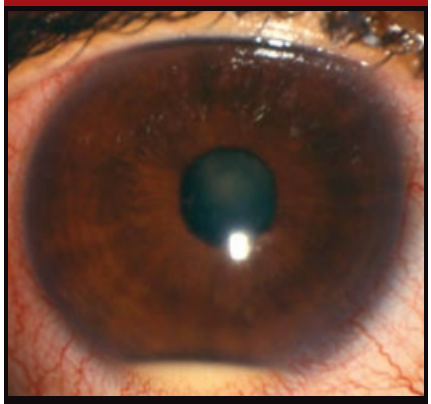
Dr. Tugal-Tutkun, who authored a comprehensive update on Behçet disease last year in the *Middle Eastern Journal of Ophthalmology*,[1] said that the diagnosis has always been problematic. There is still no specific diagnostic test for the disease, but she hopes ophthalmologists will change that. "I believe Behçet uveitis has some distinct characteristics, and we should develop ocular diagnostic criteria, as has been done for some of the other uveitic entities."

Ahmed M. Abu El-Asrar, MD, PhD, professor of ophthalmology at King Saud University in Riyadh, Saudi Arabia, agreed and noted that an international study group determined the current diagnostic criteria. These require, in all cases, recurrent oral ulcerations as an essential symptom, plus any two or more of these symptoms:

- genital ulcerations
- eye lesions
- skin lesions
- a positive pathergy test (an intracutaneous insult, such as an intradermal injection of saline or dilute histamine, which in many Behçet patients provokes a small sterile pustule.)

Dr. Abu El-Asrar also authored a related article last year, on the retinal vasculitis often associated with Behçet.[2] He said that inflammatory eye disease generally appears later than the oral ulcerations and develops in about 70 percent of Behçet patients. He added that ocular manifestations typically include recurrent attacks of anterior uveitis—with or without hypopyon—cellular infiltration and opacification of the vitreous, retinal vasculitis, retinal infiltrates and hemorrhages, inflammatory retinal vein occlusions, cystoid macular edema and disc hyperemia. He said that the major cause of Behçet-related visual morbidity are retinal vasculitis and recurrent

Ravages of Inflammation



Hypopyon in a patient with active Behçet disease.

AHMED M. ABU EL-ASRAR, MD, PHD

vaso-occlusive episodes.

Treatments Improve

Immunosuppression has been the traditional goal of treating Behçet through the use of drugs like prednisone, azathioprine, chlorambucil, cyclophosphamide, cyclosporine, colchicine, methotrexate and mycophenolate mofetil.

Unfortunately, Dr. Abu El-Asrar said, older therapies have not been very effective. "In the past, many patients with Behçet disease became blind despite the use of conventional immunosuppressive treatments, such as systemic corticorteroids, T-cell inhibitors like cyclosporine and antimetabolites such as azathioprine and mycophenolate mofetil." In fact, Dr. Tugal-Tutkun said, 20 percent of all patients with Behçet uveitis are just not responsive to conventional immunosuppressive agents. "We have reported that the estimated risk of loss of useful vision was 16 percent at five years and 21 percent at seven years in male patients."

Dr. Tugal-Tutkun said research is currently focused on the genetics of the disease and treatment with immunomodulating biologics like interferon and TNF inhibitors. "Recent Behçets studies are primarily focused on etiology, pathogenesis and treatment, especially treatment of the uveitis," she said. "There are recent whole-genome studies that will hopefully shed light on the genetic predisposition for Behçet disease because of the association with HLA-B51."

Interferon. Interferon alpha (IFN) is effective in around 90 percent of patients resistant to conventional treatment, Dr. Tugal-Tutkun said. "It is used as monotherapy or with low-dose steroids. Its major disadvantage is low tolerability. But it provides the unique possibility of inducing drug-free remission, at least in the eye, after a relatively short treatment period. I believe sustained remission may be obtained after discontinuation of IFN. Somehow the balance of the immune system may be restored for good. We still do not know the exact mechanism of action."

Dr. Tugal-Tutkun has developed a careful dosing regimen for this therapy. "In our treatment regime, the initial dose of interferon alpha 2a is 6 million international units per day given subcutaneously. After two or three weeks we taper the dose to 3 MIU per day followed by gradual tapering to 3 MIU three times a week and then to twice a week. For breakthrough attacks we increase the dose again. If the patient develops a severe attack before we reach the lowest tapered dose we consider it as treatment failure."

Infliximab. Dr. Tugal-Tutkun said that infliximab infusion shows strong efficacy in holding back the disease. One problem with infliximab is the critical therapeutic dosing. She said that the doses cannot be missed and must be done every four to six weeks, an expectation which isn't always easy for patients to fulfill. "We administer infliximab at 5 mg/kg intravenous infusion every four to six weeks. Maybe this dosing is needed because we have been using infliximab as a last resort in the most resistant cases. In one of our patients who developed resistance we had to increase the dose to 10 mg/kg every four weeks. But that is another reason why we cannot stop infliximab once we start it in our patients—there is currently no other more effective option. And another major concern with its long-term use is the development of resistance that may be associated with the development of antichimeric antibodies." The longest duration of infliximab treatment in Dr. Tugal-Tutkun's clinic was 7.5 years.

Adalimumab. Dr. Tugal-Tutkun said that adalimumab, perhaps better known for treating rheumatoid arthritis, may also calm Behçet symptoms, but she believes adalimumab falls shorts of infliximab in certain circumstances. Infliximab is better for the treatment of severe acute exacerbations because peak serum concentrations are not reached quickly enough with adalimumab. She said, however, that a steadier long-term concentration is better maintained with adalimumab. "The usual dose of adalimumab is 40 mg administered subcutaneously every other week; but resistant cases may require weekly administration."

Anti-TNF danger. As inhibitors of tumor necrosis factor, infliximab and adalimumab pose the risk of permitting the reactivation of latent pathogens, such as tuberculosis. "We screen all our patients, and those who are PPD- and/or Quantiferon-positive receive isoniazid prophylaxis," she said. "I used to use isoniazid only for nine months as recommended by the pulmonary specialists. But a couple of years ago, one of my patients developed pulmonary TB only two months after discontinuing isoniazid. Since then, I try to keep my patients on isoniazid as long as infliximab infusions are continued, at least in those with a higher risk for TB."

In terms of therapeutic algorithms, Dr. Tugal-Tutkun would like biologics to be a first-line treatment option for physicians who choose them, but she says it comes down to the health care system of each country to decide that. In Turkey, for example, "We are allowed to use biological agents only in patients refractory to or intolerant of conventional treatment."

Care Down the Road

Dr. Tugal-Tutkun said that since treatments are still imperfect, patients need to optimize their health with other measures. What they definitely should

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This year the Joint Meeting in Chicago will host ophthalmologists visiting from the Middle East, many of whom, like Drs. Tugal-Tutkun and Abu El-Asrar, bring uncommon expertise in treating Behçet disease. The Chicago Meeting will also offer an entire Subspecialty Day for uveitis presentations. Developed in conjunction with the American Uveitis Society, it will run from 8 a.m. to 5 p.m. on Saturday, Oct. 16, in McCormick Place, Room S102.

attend to is dental hygiene. "There are studies that show the effect of mouth pathogens and hygiene on the course of the disease. I advise my patients to practice regular dental care," she said.

Sometimes patients ask Dr. Tugal-Tutkun about alternative therapies, such as herbs and acupuncture. "If the patient really believes that something will help, then I tell them to keep on doing what they are doing as long as it is not something harmful or does not interfere with my treatment."

Dr. Tugal-Tutkun said, "There are still a lot of unknowns about this disease, but the low socioeconomic status of Behçet patients compared with other uveitis patients is a well-known fact, at least in my country. Improving the status of these patients will help control and hopefully eliminate the disease," she said.

Generally speaking, progress on Behçet has a long way to go. "So far the exact pathogenesis of the disease is not well-understood," Dr. Tugal-Tutkun said. "In the future, extensive basic science research may reveal the important immunologic pathways involved in triggering the disease, allowing us to develop more effective and selective biologic therapies." That is, no doubt, the hope of Sanya Richards and thousands of others with Behçet disease.

1 Tugal-Tutkun, I. *Middle East Afr J Ophthalmol* 2009;16(4):219–224.
2 Abu El-Asrar, A. M. et al. *Middle East Afr J Ophthalmol* 2009;16(4):202–218.

The physicians interviewed for this story have no related financial interests.

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The most comprehensive clinical information on Behçet disease, especially for physicians and patients new to the disease, may be that offered by the National Institute of Arthritis and Musculoskeletal and Skin Disorders at www.niams.nih.gov/Health_Info/Behcets_Disease/default.asp.