Caution Advised When Diagnosing Behçet's

ARTICLES BY SHARON WORCESTER

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – A conservative approach is best when it comes to making a diagnosis of Behçet's disease, Dr. Kenneth Calamia said at the meeting.

Although oral and genital ulcers are common in the disease, they also are a common manifestation of many other conditions, and it is important to consider the other possible causes first.

The importance of a Behçet's diagnosis doesn't have anything to do with ulcers – it has to do with the risk or presence of serious manifestations, including vascular disease, central nervous system manifestations, and uveitis, said Dr. Calamia of the department of medicine at the Mayo Clinic in Jacksonville, Fla.

"You don't want to [needlessly] give a patient the baggage of that diagnosis," he said, noting that in patients diagnosed with Behçet's, everything will be attributed to the disease for the rest of their lives.

In the United States and Europe, true Behçet's is quite rare (about 0.3-7.5 cases/100,000 population), compared with places like Turkey and other "Silk Road" areas, which have a very high prevalence (100-370 cases/100,000 population). In those areas, more severe forms are much more prevalent, and the benign mucocutaneous symptoms that comprise most of the cases in the United States are referred to as American Behçet's disease, Dr. Calamia said.

The term "Behçet's syndrome" also can be used to describe the types of cases typically seen in the United States, but in many cases, the diagnosis is actually "complex aphthosis," he said, adding that Behçet's treatment principles can nonetheless be used to help patients with this condition.

Complex aphthosis is a term used by oral dermatologists to help classify types of recurrent aphthous stomatitis. As opposed to simple aphthosis, which is characterized by episodic, short-lived lesions that are few in number, recur three to six times per year, and tend to affect nonkeratinized mucosa, complex aphthosis lesions can be continuous, numerous, large, slow-healing, and debilitating.

Keep in mind that both simple and complex aphthosis can be associated with menstruation, sprue, inflammatory bowel disease, HIV, hematologic disorders (such as cyclic neutropenia, IgA deficiency, myelodysplasia/myeloproliferation), various deficiencies (B vitamins, folate, iron, and zinc), and smoking cessation, Dr. Calamia said, explaining that smoking tends to increase keratinization, which protects against ulcers, and that protection is lost when a patient quits.

In a study conducted by an oral dermatologist several years ago, only 9% of 269 patients with severe complex aphthosis – 16% of whom also had genital ulcers – had a Behçet's diagnosis, he noted.

Some other diagnoses in the cohort included anemia in 25%, gastrointestinal disease in 16%, hematologic disorders in 5%, mucosal disease in 6%, smoking discontinuation in 4%, and drug-related ulcers in 3%.

"[Complex aphthosis] is the diagnosis I prefer in those who have mouth and genital ulcers, but nothing else to support a diagnosis of Behçet's," he said.

Consider the other possible causes of the ulcers, and also consider the differential diagnoses for recurrent aphthous stomatitis, which include recurrent intraoral herpes simplex virus, Wegener's granulomatosis, oral Crohn's disease, pyostomatitis vegetans, erythema multiforme, lichen planus, mucous membrane pemphigoid, and pemphigus vulgaris, he said.

A diffuse, widespread, and chronic presentation, which is not characteristic of recurrent aphthous stomatitis or Behçet's disease, can help differentiate between those conditions and these differential diagnoses, he said.

Dr. Calamia disclosed that he has received research support from Genentech and Celgene, and has served on an advisory board for Centocor. ■

Tx Available for Behçet's Mucocutaneous Symptoms

EXPERT ANALYSIS FROM THE CONGRESS OF CLINICAL RHEUMATOLOGY

DESTIN, FLA. – Although no agent has been approved for the treatment of Behçet's disease in the United States, several treatments have been tried in patients with mucocutaneous manifestations of the disease, said Dr. Kenneth Calamia.

Behçet's disease is relatively rare in the United States and Europe, occurring in 0.3 to 7.5 per 100,000 people, but among those affected, mucocutaneous symptoms are common, and in fact are among the hallmarks of the disease. In a study of 164 patients treated from 1985 to 1997 at the Mayo Clinic in Jacksonville, Fla., where Dr. Calamia is associate professor of medicine, 98% had oral ulcers and 80% had genital ulcers. These were the most common manifestations, he said.

According to 2008 EULAR guidelines for the treatment of Behçet's, the decision to treat skin and mucosal involvement should be based on the severity perceived by the physician and patient, and mucocutaneous involvement should be treated according to the dominant or codominant lesions present (Ann. Rheum. Dis. 2008;67:1656-62).

Topical treatments should be used first line for isolated oral and genital ulcers and acnelike lesions; colchicine should be used when the dominant lesion is erythema nodosum; and azathioprine, interferon-alpha, and tumor necrosis factor (TNF)-alpha antagonists can be considered in resistant cases, according to the guidelines.

The list of treatments used for the management of mucocutaneous manifestations includes these and other agents. One of Dr. Calamia's favorite concoctions for oral ulcers is "magic mouthwash," an elixir of half Decadron (betamethasone) syrup or Celestone syrup and half Benadryl topical anesthetic. "This can control ulcerations very well, especially if used early at the first sign of a breakout," he said. The elixir is used before meals and at bedtime, and is swished in the mouth, held as long as possible, and spit out.

According to Dr. Calamia, other treatments that have been used for mucocutaneous manifestations of Behçet's include topical steroids, which work and have a better side effect profile than do systemic treatments; topical tacrolimus, pimecrolimus, and pentoxifylline, which dermatologists particularly like; azathioprine, which works; interferon-alpha, which also works; thalidomide, which works but causes neuropathy, so it is no longer used for this disease; dapsone, which is another favorite of dermatologists; methotrexate, which is used but which he is "not personally impressed with" for mouth ulcers; colchicine, which can be used for this or any of the other manifestations of the disease; and anti-TNF agents, which are clearly of benefit.

In a randomized, placebo-controlled study of etanercept, 40% of 40 patients who received etanercept were ulcer free at 4 weeks, compared with just 5% of those who received placebo. There was a significant reduction in oral ulcers, modular lesions, skin lesions, and arthritis attacks at 4 weeks, he said (J. Rheum. 2005;32:98-105).

"There's no question that anti-TNF drugs do work, but it is probably best to try nonbiologics in these patients, especially for mucocutaneous disease," said Dr. Calamia, who disclosed that he has received research support from Genentech and Celgene and served on an advisory board for Centocor. ■

IgG4-Related Systemic Aortitis Responds to Rituximab

EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

CHICAGO – Rituximab is showing promise as an effective treatment for IgG4-related aortitis, a condition which has only recently been described.

In one patient with aortitis and a high serum IgG4 level of 1,560 mg/dL, treatment with rituximab resulted in a decrease to 390 mg/dL within 2 months. Currently the patient's serum IgG4 level is 26 mg/dL (normal is below 135 mg/dL), Dr. John H. Stone reported.

Remarkably, the treatment appears to affect only IgG4 and not other IgG subclasses, suggesting that the agent is depleting CD20-positive B cells that evolve into the short-lived plasma cells which produce this antibody, and thus making a good case that this process is pathologic, said Dr. Stone, director of clinical rheumatology at Massachusetts General Hospital, Boston.

In another aortitis patient who had been treated with steroids but couldn't tolerate the side effects – and whose IgG4 levels increased when the steroids were discontinued – rituximab had an equally abrupt effect. At 1 month following treatment, her IgG4 levels had fallen to 31 mg/dL. And in a 68-year-old man who previously responded to steroids, but who flared and was being treated with various disease-modifying antirheumatic drugs, serial rituximab decreased his IgG4 level with each dose until it normalized.

Remarkably, the treatment appears to affect only IgG4 and not other IgG subclasses.

DR. STONE

Ten patients with aortitis, including seven with IgG4 elevation, have been treated with rituximab as part of this series, and IgG4 levels declined quickly in all seven, while all other IgG subclasses remained stable, he said.

IgG4-related aortitis was first described in 2009 by Dr. Stone and his colleagues, who published on the case of a 67-year-old patient who developed dissection of the ascending aorta in the setting of IgG4-related disease, thereby linking IgG4-related systemic disease with this newly recognized subset of noninfectious aortitis, and adding to a growing list of conditions, such as autoimmune pancreatitis, that are associated with IgG4-related systemic disease.

At surgery, a transmural lymphoplasmacytic infiltrate was detected in the aorta, and on immunohistochem-

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ical studies more than 50% of plasma cells in the lesion stained for IgG4. The patient's IgG4 levels were elevated nearly 10-fold, and reevaluation of a lymph node biopsy performed 4 years earlier showed previously undetected IgG4-related systemic disease (Arthritis Rheum. 2009;60:3139-45).

Dr. Stone and his colleagues concluded that IgG4-related systemic disease should be considered in all patients with aortitis of unknown etiology, and noted that treatment might prevent progression of the systemic disease to other organs.

At the ACR symposium, where he spoke on "odd types of vasculitis," Dr. Stone said it is intriguing that this condition hadn't been previously identified given the number of other diagnoses known to be related to IgG4.

The findings prompted a review of prior cases of aortitis at Massachusetts General Hospital, where a large number of aortic surgeries are performed, and it was found that 5.2% of 638 thoracic aorta resections performed from 2003 through 2008 were inflammatory, and about 12% stained intensely for IgG4, he said.

"So we think [IgG4-related systemic disease] accounts for about 12% of cases of inflammatory aortitis," he added, noting that in a 2008 study from Japan, 4 of 10 cases involving the descending aorta stained intensely for IgG4.

The findings demand that the classification of aortitis be revisited, and that lymphoplasmacytic IgG4-related disease be included as a type of isolated aortitis, Dr. Stone concluded.

Dr. Stone said that he had no relevant financial disclosures. ■

Prolonged Glucocorticoid Use May Prevent Vasculitis Relapse

BY AMY ROTHMAN SCHONFELD

FROM A RHEUMATOLOGY MEETING SPONSORED BY NEW YORK UNIVERSITY

NEW YORK – Early discontinuation of glucocorticoid therapy may greatly increase the risk of relapse in antineutrophil cytoplasmic antibody–associated vasculitis, said Dr. Yusuf Yazici.

He discussed a study that addressed the controversial question of whether low-dose glucocorticoids contribute to maintaining remission of the disease.

Patients successfully treated for antineutrophil cytoplasmic antibody–associated vasculitis (AAV) face high rates of relapse, up to 38% at 30 months. Although glucocorticoids are often used to prevent relapse in AAV, high-quality evidence to guide treatment is lacking, Dr. Yazici said.

"Our aim is always to get patients off steroid therapy, but maybe that is a misguided aim," said Dr. Yazici, director of the Seligman Center for Advanced Therapeutics and Behçet's Syndrome Evaluation, Treatment and Research Center at the New York University Hospital for Joint Diseases.

Dr. Yazici cited findings from a meta-analysis of studies investigating the treatment of AAV that included a predefined glucocorticoid dose and protocol for tapering (Arthritis Care Res. 2010;62:1166-73). Thirteen studies involving 983 patients were identified for inclusion, including five observational and eight randomized controlled trials. None of the studies directly compared glucocorticoid regimens.

To elucidate the role of glucocorticoid therapy in relapse, the authors divided the studies into those that had a zero glucocorticoid target dose (aimed to get patients completely off glucocorticoid therapy, n = 695) and those having a nonzero glucocorticoid target dose (low glucocorticoid maintenance dose allowed, n = 288).

The investigators found that 36% of the overall group relapsed. Upon further examination, the relapse rate was 43% for those in the zero glucocorticoid target dose group, compared with 14% in those allowed to continue glucocorticoids – approximately a threefold increase.

Even for those who discontinue glucocorticoids, timing is important. When the investigators divided patients in the zero target dose into those who had to reach zero within 12 months (the early zero group) and those who were allowed to reach zero after 12 months (the late zero group), there was a 48% relapse rate for the early zero group, compared with a 29% rate for the late zero group. While the early zero glucocorticoid target dose group had significantly more relapses than the nonzero group (*P* less than .001), the late zero glucocorticoid target dose group was similar to the nonzero group. By grouping the late zero and nonzero groups, the authors concluded that early discontinuation of glucocorticoid was associated with a 20% increased risk of relapse (28% vs. 48%).

The results suggest that glucocorticoid dose should be monitored, and that patients with AAV should be kept on 5.0-7.5 mg of glucocorticoids for at least a year after reaching remission, said Dr. Yazici. ■

VITALS

Major finding: The relapse rate for patients with antineutrophil cytoplasmic antibody–associated vasculitis was 43% in a pooled analysis of studies in which patients were tapered completely from glucocorticoids, compared with 14% in studies of patients allowed to continue glucocorticoid therapy. Early discontinuation was associated with a higher relapse rate than was later discontinuation.

Data Source: Meta-analysis of 13 studies involving 983 patients investigating the treatment of AAV that included a predefined glucocorticoid dose and protocol for tapering.

Disclosures: Dr. Yazici has served as a consultant or speaker for, or has received research support from, BMS, Celgene, Centocor, Genentech, Merck, Novartis, Roche, and UCB.

Use Topicals for Less Severe Cutaneous Lupus

BY SHARON WORCESTER

EXPERT ANALYSIS FROM A SYMPOSIUM SPONSORED BY THE AMERICAN COLLEGE OF RHEUMATOLOGY

CHICAGO – A number of treatments can be considered for cutaneous lupus erythematosus.

"Topicals are certainly a good way to start for a less severe patient," Dr. Victoria P. Werth said at the meeting.

Topical steroids can be used, she said, noting that she often starts with a potent class 1 drug.

A class 1 drug, however, would be impossible to use on the face for more than a few days, added Dr. Werth, a dermatologist and immunologist at the University of Pennsylvania, Philadelphia.

"Often on the face we use Cortaid or something like a Synalar [fluocinolone] or Lidex [fluocinonide] for a short period of time and then taper down to hydrocortisone," she said.

The more recently available topical nonsteroidal T-cell inhibitors, tacrolimus and pimecrolimus, can be used as adjunctive therapy. These agents aren't perfect, but they may be worth trying in a patient in whom one does not want to use steroids long term, she said.

Intralesional steroids are another treatment option and are particularly useful for scalp lesions and isolated lesions.

Vitamin D replacement also may be helpful. A study published last year showed that cutaneous lupus patients, like many people, had very low vitamin D levels in winter, but levels didn't rise much during the summer as they do in others – likely because patients are following advice about sun avoidance.

As for systemic therapy, data from prospective randomized controlled trials are lacking, and most guidance comes from retrospective case series. But antimalarials are considered first-line treatment in those who can't use topical therapy.

Specifically, hydroxychloroquine is typically given at 6.5 mg/kg per day or less for 6-8 weeks, and quinacrine can be added at 100 mg/day for an additional 6-8 weeks in those who fail to respond to hydroxychloroquine monotherapy.

Not everyone needs the combination, but it is very beneficial in some patients, Dr. Werth noted.

Chloroquine at 3.5 mg/kg per day can be used in those who fail to respond to that combination. Although there are more concerns about toxicity, there are patients who will do better on chloroquine, she said.

Other therapies beyond the topicals and antimalarials include dapsone, retinoids, thalidomide, methotrexate, mycophenolate mofetil, azathioprine, corticosteroids, and cyclophosphamide.

"We use dapsone predominantly for bullous lupus, and in some patients – if they're not too sick with their SLE, and their bullous lupus is not terrible – it's worth trying," she said, noting that "it's very good on neutrophilic infiltrates, and it can work."

Retinoids are on the list only because one trial compared them with antimalarials. Retinoids aren't very effective, they have a lot of toxicity, and they're not easy to use, she said.

In contrast, thalidomide can be very effective and is used in refractory patients. Its use is associated with rapid clinical response at 100 mg/day for 2 weeks, with full clinical response in 2-3 months. About 75% of patients who are refractory to antimalarials will respond.

Maintenance doses also can be effective (25-50 mg/day), but rapid relapse can occur on discontinuation.

Thalidomide does not have much effect on systemic lupus. Its use is associated with the risk for serious toxicity, including teratogenicity, neurotoxicity, premature ovarian failure, and hypercoagulable state.

Methotrexate, mycophenolate mofetil, and azathioprine have been shown to be equivalent to thalidomide in many ways, and because they aren't associated with the neurotoxicity that can occur with thalidomide, Dr. Werth said she often uses one of these first.

"I don't really have a preference for one over another," she added.

She noted, however, that it is important to consider what else may be going on with patients, because those with renal involvement can be treated with mycophenolate mofetil or cyclophosphamide, and both may also help with cutaneous disease.

In addition to medical therapies, patients with cutaneous disease should be advised to avoid heat and drug exacerbations of their condition. It is critical that they use a high SPF sunscreen with good UVA and UVB coverage. Many sunscreens will say they offer both, but most don't have great UVA coverage, Dr. Werth said.

Tell patients to look for a product that has the highest SPF they can find (at least 30), and to ensure that the product contains ecamsule (Mexoryl) or avobenzone/oxybenzone (Helioplex) to provide good UVA protection, she advised.

Dr. Werth disclosed that she has received grants from Celgene Corporation and Amgen, and has served as a consultant to MedImmune, Genentech, Novartis, Pfizer, and Cephalon. She also developed an outcome measure for lupus. ■