Be Alert to CNS Symptoms With TNF-α Blockade

In patients with family histories or other risk factors for multiple sclerosis, use TNF blockers cautiously.

BY BRUCE K. DIXON
Chicago Bureau

CLEVELAND — Tumor necrosis factor–α blockade should not be instituted in patients with known multiple sclerosis and should be used with caution in patients with family histories or other risk factors for MS, according to Jeffrey A. Cohen, M.D., a neurologist at the Cleveland Clinic.

In addition, physicians should be alert to uncommon central nervous system manifestations in patients receiving tumor necrosis factor (TNF) blockade for their inflammatory diseases, he said at a meeting on the treatment of autoimmune and inflammatory disorders.

'I would not obtain an MRI unless there was some clinical suggestion of potential [for MS].'

DR. COHEN

TNF inhibitors currently approved by the Food and Drug Administration include the monoclonal antibodies infliximab (Remicade) and adalimumab (Humira) and the fusion protein etanercept (Enbrel).

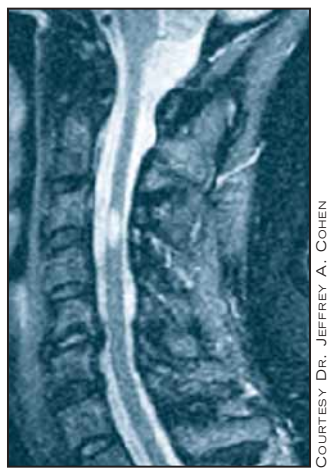
TNF blockade both prevents and abrogates demyelinating disease in vitro and in animal studies. However, in humans, TNF blockade actually increased MS activity, said Dr. Cohen, citing data from two studies of infliximab and the discontinued lenercept. "In addition, treatment of other diseases for which TNF inhibitors are highly effective, including rheumatoid arthritis, Crohn's disease, and psoriasis, on rare occasions leads to CNS inflammatory demyelinating syndromes," said Dr. Cohen at a summit sponsored by the Cleveland Clinic.

Failure of a TNF antagonist therapy in MS may be due to pleiotropic aspects of TNF actions, he noted. "In the CNS, TNF mediates cellular apoptosis and tissue damage, has important immunoregulatory functions, and is involved in tissue repair and regeneration. This experience reminds us that in the development of novel therapeutics, one must be cautious in extrapolating from animal models to human disease and from the results in one human disease to another," he said.

Discussion of restarting therapy in patients who have been taken off a TNF inhibition because they developed a CNS manifestation involved a hypothetical case representing a composite of patients created for teaching purposes: a 32-year-old woman with a 5-year history of active Crohn's disease unresponsive to 6-mercaptopurine, mesalamine (Pentasa), and budesonide. She was started on infliximab and responded after the third infusion with complete resolution of abdominal pain and cramping and with a marked reduction in the frequency of bowel movements.

"After 12 months of therapy, she developed gait imbalance and numbness and tingling of the hands and feet that worsened over several weeks, making it difficult for her to walk," Dr. Cohen said. The patient's Crohn's disease remained quiescent. A cranial nerve exam was normal, and the woman had normal strength, mild spasticity in the legs, diffuse hyperreflexia with right Babinski's sign, mild ataxia of the arms and legs, decreased position sense in the hands and feet, and moderate gait ataxia.

The patient's erythrocyte sedimentation rate was 55, she did not have a lupus anticoagulant, her B_{12} and copper were normal, and an antibody test was negative. An MRI of the cervical spine showed an ovoid lesion in the spinal cord at C3-4 with mild diffuse enhancement. A lumbar puncture showed mild mononuclear cell pleocytosis, normal glucose, mildly elevated protein, normal IgG index, and no oligoclonal bands Dr. Cohen said.



COURTESY DR. JEFFREY A. COHEN

An MRI showed an ovoid lesion in the spinal cord.

Infliximab therapy was discontinued, and the woman was treated with intravenous methylprednisolone for three days, with the dose tapered over 2 weeks. "Within 12 weeks, the neurologic symptoms had completely resolved," said Dr. Cohen. "Repeat MRI showed resolution of enhancement of the spinal cord lesion and no other lesions in the brain or spinal cord. Her original Crohn's symptoms recurred, however, and did not respond to MTX [methotrexate] or budesonide. Her symptoms improved on prednisone 60 mg/day but returned when the dose was tapered. She said she had felt much better on infliximab and asked about the possibility of restarting it," said Dr. Cohen. "The decision to restart infliximab must be based on weighing the risks from Crohn's disease and whether other treatment options exist versus the risk of a recurrent neurologic complication."

"The differential diagnosis of neurologic manifestations in patients with immune mediated inflammatory disorders treated with TNF inhibitors is broad and includes neurologic complications of the underlying disease, neoplastic or infectious complications of TNF inhibitors, and direct neurologic complications of TNF inhibitors. Reported neurologic complications of TNF inhibitors include CNS demyelinating syndromes, aseptic meningitis, seizures, ischemic optic neuropathy, and demyelinating peripheral neuropathies," according to Dr. Cohen.

"CNS demyelination can occur anytime after an anti-TNF agent is started, and clinical manifestations reflect the anatomic site of involvement. Demyelination has been reported with all TNF antagonists and thus appears to be a class effect."

In terms of the nervous system, Dr. Cohen recommends avoiding TNF blockade for patients who are known to have MS or who might be at risk of MS; nor should TNF inhibitor infusions be given to patients who have had a previous clinically isolated CNS syndrome without the formal diagnosis of MS or to patients who have cranial MRIs that look suggestive of MS but do not yet have clinical manifestations, advised Dr. Cohen.

"If you're forced to use TNF blockade because your patient has inflammatory bowel disease, RA [rheumatoid arthritis], or psoriasis that is not responding well to other [treatments], you need to watch closely for potential CNS demyelination, and that should include both clinical monitoring and periodic MRI. If a patient develops a CNS complication, TNF blockade should be interrupted and the investigation should include neurologic assessment to clarify the nature of the complication. That evaluation should include lumbar puncture, and treatment should include a corticosteroid. If the patient continues to have CNS demyelinating events following discontinuation of TNF blockade, you've probably unmasked incipient MS, in which case I would consider disease-modifying therapy for MS," Dr. Cohen said.

The neurologist advised against looking for MS in every patient prior to starting a TNF inhibitor for treatment of inflammatory bowel disease, rheumatoid arthritis, or psoriasis. "In particular, I would not obtain an MRI unless there was some clinical suggestion of potential [for MS]." However, uveitis is a different story: "Uveitis is a manifestation that can occur in MS, so I would look very carefully for any indication of MS involvement" before beginning TNF blockade. ■

Intraarticular Hylan Injections Benefit Patients With Hip OA

BY BRUCE JANCIN
Denver Bureau

VIENNA — Ultrasound-guided intraarticular injection of hylan G-F 20 (Synvisc) in patients with hip osteoarthritis is safe, well tolerated, and results in reduced pain and improved function for up to 9 months post injection, Alberto Migliore, M.D., reported at the annual European Congress of Rheumatology.

Synvisc, a hyaluronan derivative, is injected in order to supplement synovial fluid that has lost its elastoviscosity due to osteoarthritis.

It is used routinely in patients with symptomatic knee osteoarthritis, a setting in which multiple studies have shown that the treatment provides pain relief with a low risk of adverse events.

Fewer data are available regarding Synvisc in hip osteoarthritis, in large part because hip injections are technically more difficult and require ultrasound guidance in order to achieve consistently good results, explained Dr. Migliore of San Pietro Hospital, Rome.

He reported on 223 patients with symptomatic hip osteoarthritis who received one or more intraarticular 2-mL Synvisc injections.

Sixty-two had bilateral hip osteoarthritis. Patients were followed for up to 9 months. They could receive a repeat injection every 3 months as needed. A total of 360 injections were administered.

Nineteen patients left the study in order to undergo hip replacement surgery.

Significant improvement occurred in all three study end points: osteoarthritis pain as self-assessed on a visual analog scale, need for nonsteroidal anti-inflammatory drugs, and clinical improvement as measured using the Lequesne index. (See chart.)

Outcomes Following Ultrasound-Guided Synvisc Hip Injection

	Baseline	3 months	6 months	9 months
Osteoarthritis pain (10-point visual analog scale)	6.2	4.0	4.4	4.8
Mean NSAID use (days per month)	9.5	4.4	4.9	6.7
Lequesne index	10.1	6.4	7.0	7.8

Source: Dr. Migliore

No local infections or systemic adverse events occurred.

The injection technique involved the use of a sterile biopsy guide attached to a 3.5-MHz convex or 7-MHz linear ultrasound transducer. The joint was imaged using an anterior parasagittal approach.

Now that the safety and efficacy of intraarticular Synvisc injections have been demonstrated in hip osteoarthritis, Dr. Migliore's next goals are to establish the optimal dosing regimen and determine whether the therapy exerts a disease-modifying effect. ■