Possible Link between Infliximab and Optic Neuritis

Joseph Pikkel MD

Department of Ophthalmology, Ziv Hospital, Safed, Israel

Key words: infliximab, optic neuritis, tissue necrosis factor

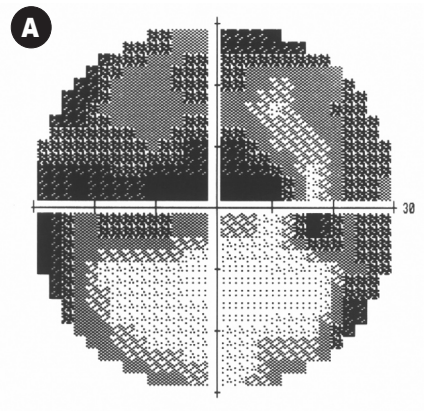
IMAJ 2008;10:477–478

Tumor necrosis factor is a cytokine derived from macrophages and is believed to stimulate the inflammatory process by binding to cell surface receptors. Infliximab is a chimeric antibody of the immunoglobulin G class, which binds TNF1 and inhibits its activity [1]. The use of infliximab for inhibition of inflammatory processes has been increasing in recent years and is now widely used for the treatment of rheumatoid arthritis, Crohn's disease and other conditions including severe persistent uveitis.

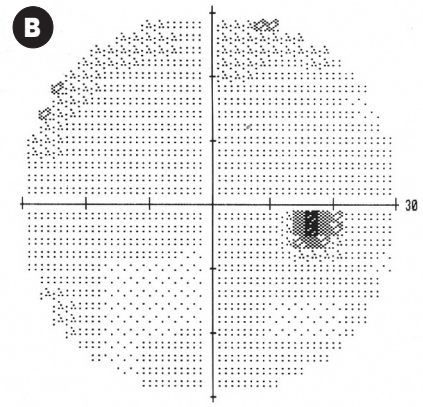
Cytokine-targeted therapy has generally been reported to be safe, although headache and respiratory congestion may occur. Reports of a possible link between infliximab and exacerbation of preexisting demyelinating diseases and retrobulbar optic neuritis have been published in recent years [2]. We present here the case of a 39 year old woman with rheumatoid arthritis who developed optic neuritis while being treated with infliximab. Although the optic neuritis may have been coincidental, we believe that use of the drug during development of the disease, together with the current literature on the subject, support our conclusion that the optic neuritis was associated with infliximab.

Patient Description

A 39 year old woman with a 4 year history of rheumatoid arthritis and obesity was admitted to our hospital for treatment because of pain mainly in her knees. She was treated with methotrexate and infliximab 3 mg/kg i.v. (total of 300 mg of infliximab i.v. per treatment). Three days after the first infliximab treatment she complained of a rapid and sudden deterioration of vision and pain in her right eye while moving her eyes in different directions.



[A] Visual field of the right eye at hospitalization.



[B] Visual field of the right eye are month after discharge.

On admission best-corrected visual acuity was 20/200 in her right eye and 20/20 in her left eye. The intraocular pressure was 16 mmHg in both eyes. Eye movements were full to all directions. She identified 4 of 14 Ishihara pseudoisochromatic plates with her right eye and 14 of 14 in her left eye. In the right eye she had a relative afferent pupillary defect. There was some nerve fiber layer thinning at the inferior temporal region of the disk. The left optic disk was normal. Perimetry of her right eye showed superior altitudinal visual field defect [Figure A]. Perimetry of the left eye was normal. Computed tomography scans were normal. Magnetic resonance imaging scans showed enhancement and enlargement of the right optic nerve and some small lesions around the brain ventricles with no enhancement.

Suspecting that the optic neuritis was associated with infliximab we stopped the treatment with infliximab and started treatment with i.v. methylprednisone 250 mg four times a day, followed by a dose of oral prednisone over the next 10 days. Within 2 weeks the patient's right eye visual acuity returned to 20/40 and the relative afferent pupillary defect disappeared. Color vision was 13 of 14 Ishihara pseudoisochromatic plates. The patient's visual field deficit resolved [Figure B].

Comment

The patient's clinical course was consistent with optic neuritis. Differential diagnosis of the cause of optic neuritis might be activation of latent multiple sclerosis, use of toxic drugs (like isoniazid, interferon-alpha and ethambutol), and infectious diseases (such as Lyme disease, tuberculosis, syphilis, human immunodeficiency virus, hepatitis B, herpes and cytomegalovirus). There was no history of previous drug consumption or any infectious disease, nor did the patient have positive serology to any of the above. There is a very strong association between optic neuritis and multiple sclerosis, but the patient had no neurological symptoms or previous diagnosis of multiple sclerosis. Onset of the patient's visual symptoms was within

days from the beginning of treatment with infliximab, suggesting a relationship between the infliximab treatment and the onset of optic neuritis.

The link between infliximab, the appearance of neurological symptoms and exacerbation of demyelinating nerve diseases was described previously. Robinson et al. [3] suggested that TNF antagonists might increase autoimmune activity and enhance demyelination. Fernandez-Arquero and collaborators [4] found a primary association between susceptibility to multiple sclerosis and polymorphism of the TNF gene. Nash and Florin [5] reported other side effects of infliximab, such as increased risk of lymphoproliferative disease, the development of lupus-like syndromes and demyelination, including optic neuritis and reactivation of multiple sclerosis.

Our patient had no physiological factors that could predispose to the development of optic neuritis. Furthermore, there was a close temporal correlation between exposure to the drug and the onset of symptoms. After discontinuation of infliximab therapy and treatment with steroids, the patient's condition improved.

Due to the increasing use of infliximab therapy and the possible relationship between infliximab and optic neuritis, we should be aware of this adverse effect and closely monitor these patients for the development of optic neuritis and other neurological signs and effects.

TNF = tumor necrosis factor.

References

1. Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. *Intern Med* 2001;134:695–706.
2. Foroozan R, Buono LM, Sergott RC, Savino PJ. Retrobulbar optic neuritis associated with infliximab. *Arch Ophthalmol* 2002;120: 985–7.
3. Robinson WH, Genovese MC, Moreland LW. Demyelinating and neurologic events reported in association with tumor necrosis factor alpha antagonism. *Arthritis Rheum* 2001;44:1977–83.
4. Fernandez-Arquero M, Arroyo R, Rudio A, et al. Primary association of TNF gene polymorphism susceptibility to multiple sclerosis. *Neurology* 1999;53:1361–3.
5. Nash PT, Florin TH. Tumor necrosis factor inhibitors. *Med J Aust* 2005;183:205–8.

Correspondence: Dr. J. Pikkel, 8 Etrog Street, Caesarea, Israel.
Phone: (972-4) 636-04630
Fax: (972-4) 682-8647
email: pikel.y@ziv.health.gov.il