CONCISE REPORT

Optic neuritis occurring with anti-tumour necrosis factor α therapy

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Objective: Various demyelinating disorders have been reported in association with anti-tumour necrosis factor α (TNF α) agents. The objective of this study was to review the occurrence, clinical features and outcome of optic neuritis (ON) during treatment with anti-TNF α agents.

Methods: A PubMed search was conducted to identify literature addressing the potential association between anti-TNF α agents and ON, following our experience with a patient having rheumatoid arthritis in whom ON developed while being treated with infliximab.

Results: 15 patients including the case presented here with ON in whom the symptoms developed following TNF α antagonist therapy were evaluated. Eight of these patients had received infliximab, five had received etanercept and two patients had received adalimumab. Among them, nine patients experienced complete resolution, and two patients had partial resolution, while four patients continued to have symptoms.

Discussion: Patients being treated with a TNF α antagonist should be closely monitored for the development of ophthalmological or neurological signs and symptoms. Furthermore, consideration should be given to avoiding such therapies in patients with a history of demyelinating disease. If clinical evaluation leads to the diagnosis of ON, discontinuation of the medication and institution of steroid treatment should be a priority.

Anti-tumour necrosis factor α (TNF α) agents have come into widespread use, and an increasing number of patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease are being successfully treated with this new generation of biological agents. Although rare, several reports of new onset or exacerbation of demyelinating disorders have been noted following treatment with TNF α antagonists, and continued observation is warranted in patients on these agents for the development of such diseases.¹ The demyelinating disorders that have been reported to be associated with TNF α antagonist therapy are variable, and include multiple sclerosis (MS), optic neuritis (ON), transverse myelitis and Guillain-Barré syndrome.^{2–4}

The medical rubric "optic neuritis" is possibly more a clinical syndrome than an isolated disease and can be caused by a variety of infectious, inflammatory, demyelinating, metabolic, toxic, nutritional, vascular and hereditary aetiologies. In particular, acute demyelinating ON is one of the most frequently encountered optic neuropathies in clinical practice, and is best known for its association with MS. However, acute demyelinating ON can also occur as an isolated episode without any progression.⁵

A review of the Adverse Events Reporting System database of the Food and Drug Administration in 2001 identified 20 cases of demyelinating disorders following treatment with anti-TNF α agents for arthritis. ON was reported to be the second most

common presentation (8 of 20), and it was the sole presenting symptom among two of them.²

We describe a patient with rheumatoid arthritis who developed retrobulbar ON while she was concurrently being treated with infliximab and isoniazid. We also reviewed the cases of TNF α antagonist-associated ON reported to date in the medical literature.

PATIENTS AND METHODS

We conducted a medical literature search in PubMed and identified 14 cases of ON occurring in patients receiving TNF α antagonist therapy.^{6–13}

Index patient

The patient was a 31-year-old woman with a 4-year history of seropositive rheumatoid arthritis in whom the disease had failed to respond to methotrexate, sulphasalazine, leflunomide and oral prednisolone alone and in combination at full doses. Due to her active, treatment-resistant rheumatoid arthritis, treatment with etanercept was considered. In order to rule out latent tuberculosis infection, a chest x-ray and tuberculin skin test were performed according to the standard guidelines. The tuberculin skin test was found to be positive, while no abnormalities were detected on chest x-ray. Accordingly, she was given isoniazid 300 mg once daily 3 weeks prior to the institution of etanercept treatment. In June 2005, treatment with etanercept was initiated as 25 mg twice weekly by subcutaneous injection, and all other medications except isoniazid were discontinued. However, after the fourth dose of etanercept, her regimen was switched to infliximab owing to the development of a severe injection site reaction with etanercept. Infliximab was administered intravenously in doses of 3 mg/kg body weight at weeks 0, 2 and 6, and then at 8-weekly intervals. After three doses of infliximab, dramatic improvement in her clinical condition occurred.

In December 2005, 4 weeks following the fourth dose of infliximab, the patient noticed defects in her visual field, reduced perception of brightness and pain with ocular movement, affecting the left eye, which gradually worsened over the ensuing week.

Ophthalmological examination was highly suggestive of ON (tables 1 and 2). Visual evoked potentials (VEPs) were found to be reduced in the left eye with prolonged latency, compatible with ON. Contrast-enhanced MRI of the brain and orbits as well as the electroretinogram were normal, as was intravenous fluorescein angiography. Treatment with infliximab and isoniazid was terminated considering the potential visual adverse reactions associated with both drugs. She was given three pulses of 1000 mg of intravenous methylprednisolone daily for three consecutive days, followed by 60 mg/day of oral

Abbreviations: CNS, central nervous system; MS, multiple sclerosis; ON, optic neuritis; TNF, tumour necrosis factor; VEP, visually evoked potential.

prednisolone, which was then tapered to termination within 3 weeks. One month after the cessation of the offending drugs and initiation of prednisolone therapy, computerised perimetry showed complete resolution of visual field defects in the affected eye. At that time, VEP testing disclosed improved responses, but latency in the affected eye was still longer than in the other eye. No further deterioration or relapse was noted during the follow-up, and, VEP and visual field investigations at 12 months were entirely normal.

RESULTS

To date, 15 cases of isolated ON including the case presented here, without additional neurological findings, possibly associated with TNF α antagonists have been reported in the literature.^{6–13} Eight of these patients had received infliximab, five had received etanercept, and two patients had received adalimumab. Clinical summaries of these patients are provided in table 1. The median interval from the first administration of TNF α antagonist treatment to the onset of ON was 7.5 months (range 2 months to 1.5 years).

Findings at ophthalmological examination are summarised in table 2. Brain MRIs were reported for eight of 15 patients. Among them, two disclosed a pattern compatible with demyelination in different areas of the central nervous system (CNS).

All patients but one received treatment for ON, which included pulse steroids followed by oral steroids. Nine patients experienced complete resolution, and two patients

had partial resolution of ON. Four patients continued to have symptoms.

It is of interest to note that three patients (cases 3, 4 and 5) in whom the symptoms continued without recovery had bilateral anterior ON which is not very representative of acute demyelinating ON.⁹ Those three patients had capillary dilation and vascular leakage as well as swelling in both optic nerve heads, which are more suggestive of an ischaemic or toxic form of ON.⁹ Treatment with anti-TNF agents was not discontinued in two patients. One of these patients experienced a partial resolution, while the other continued to have symptoms during the follow-up of 4 and 6 months, respectively.

DISCUSSION

TNF α has been thought to play a significant role in the pathogenesis of inflammatory demyelinating disease of the CNS. It has been demonstrated in experimental autoimmune encephalomyelitis that inhibiting the biological activity of TNF α prevents the development of demyelinating lesions in the CNS. However, surprisingly, anti-TNF agents were found to be ineffective in the treatment of MS in humans. This paradoxical failure of anti-TNF agents in MS and in the precipitation of demyelinating events may be explained by several mechanisms including heterogeneity of the role and mechanism of action of TNF α in diverse autoimmune diseases, inability of these agents to pass through the blood–brain barrier to neutralise and prevent local TNF α -mediated tissue

Table 1 Clinical characteristics and outcome of the patients who developed optic neuritis during anti-tumour necrosis factor α therapy

Case	Reference	Age and sex	Indication	Anti-TNF agent	Duration of therapy	Ocular involvement	MRI findings	Therapy	Outcome
1	Strong ⁷	45 F	Crohn's	Infliximab	10 months	UR	Normal	Pulse MP*	Complete recovery at 3 months
2	Foroozan ⁸	55 F	RA	Infliximab	13 months	UR	Mild enhancement of orbital portion of the optic nerve	Pulse MP*	Complete recovery at 3 weeks
3	ten Tusscher ⁹	54 M	RA	Infliximab	3 months	BA	NR	Pulse MP	Continued symptoms without recovery
4	ten Tusscher ⁹	62 F	RA	Infliximab	3 months	BA	NR	Pulse MP	Continued symptoms without recovery
5	ten Tusscher ⁹	54 M	RA	Infliximab	2 months	BA	NR	Pulse MP	Continued symptoms without recovery
6	Mejico ¹⁰	50 F	Crohn's	Infliximab	NR	UR	Enhancement of retro-orbital portion of the optic nerve	No treatment	Complete recovery at 6 weeks
7	Tran ¹¹	45 F	RA	Infliximab	11 months	UR	Normal	Pulse MP*	Complete recovery at 3 months
8	Index case	31 F	RA	Infliximab	4 months	UR	Normal	Pulse MP*	Complete recovery at 1 month, no recurrence at 12 months
9	Tauber ¹²	12 F	JIA	Etanercept	2.5 months	UA	NR	Pulse MP	Complete recovery at 3 months, no recurrence at 18 months
10	Tauber ¹²	17 F	JIA	Etanercept	8 months	UA	NR	Pulse MP*	Complete recovery at 2 months, no recurrence at 20 months
11	Tauber ¹²	21 F	JIA	Etanercept	18 months	BR	NR	Pulse MP	Continued symptoms while continuing etanercept at 6 months
12	Tauber ¹²	18 M	JSpA	Etanercept	11 months	UR	NR	Pulse MP	Complete recovery at 1 week, no recurrence at 14 months
13	Noguera-Pons ⁶	55 M	RA	Etanercept	3 months	BA	Demyelinating lesions at periventricular and perisylvian region	Pulse MP*	Partial recovery as improved VA of OD at 6 months
14	Chung ¹³	55 M	PsA	Adalimumab	4 months	UR	Enhancement of intracranial portion of the optic nerve	Pulse MP*	Complete recovery at 1 week, no recurrence at 12 months
15	Chung ¹³	40 M	RA	Adalimumab	12 months	UR	Mild enhancement of orbital portion of the optic nerve, demyelinating plaques at periventricular and C-spine localisation	No treatment	Partial recovery while continuing adalimumab at 4 months

BA, bilateral anterior; BR, bilateral retrobulbar; F, female; JIA, juvenile idiopathic arthritis; JSpA, juvenile spondyloarthritis; M, male; MP, methylprednisolone; *followed by tapering dose of oral prednisone; NR, not reported; OD = right eye; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNF, tumour necrosis factor; UA, unilateral anterior; UR, unilateral retrobulbar; VA, visual acuity.

Table 2 Findings at ophthalmological examination of the reported cases

Case	Reference	Pain with EOM	Visual acuity	RAPD	Colour vision	Visual field	Fundoscopy	VEP
1	Strong ⁷	Yes	OS: 20/70	Positive	NR	OS: cecocentral scotoma	OS: trace oedema of the optic nerve	NR
2	Foroozan ⁸	Yes	OS: 20/50	Positive	Abnormal	OS: superior altitudinal defect	Normal	NR
3	ten Tusscher ⁹	No	OD: 20/30; OS: 20/30	NR	NR	OD: inferior altitudinal defect; OS: inferior altitudinal defect	OD: swollen optic disc; OS: swollen optic discs	NR
4	ten Tusscher ⁹	No	OD: 20/40; OS: 20/80	NR	NR	OD: cecocentral scotoma; OS: central scotoma	OD: swollen optic disc; OS: swollen optic disc with haemorrhage	NR
5	ten Tusscher ⁹	No	OD: 20/400; OS: 20/100	NR	NR	OD: cecocentral scotoma; OS: central scotoma	OD: swollen optic disc; OS: swollen optic discs	NR
6	Mejico ¹⁰	Yes	NR	NR	NR	OS: superior altitudinal defect; OD: superior depression	Normal	NR
7	Tran ¹¹	Yes	OS: 0.3	Positive	Abnormal	OS: paracentral scotoma	Normal	Prolonged latency
8	Index case	Yes	OS: 20/20	Positive	Abnormal	OS: superior altitudinal defect	Normal	Reduced with prolonged latency
9	Tauber	No	OD: 6/60	NR*	Abnormal	NR*	OD: inflammatory cells in the vitreous with a swollen optic disc†	Reduced with prolonged latency
10	Tauber ¹²	No	OD: phthisic; OS: 6/18	NR‡	NR*	NR*	OD: swollen optic disc	NR
11	Tauber ¹²	No	OD: 6/24; OS: 6/24	Negative	Abnormal	NR§	Normal	Prolonged latency
12	Tauber ¹²	Yes	OD: finger counting at 20 cm	NR*	NR*	NR*	OD: inflammatory cells in the vitreous with a swollen optic disc†	Reduced with prolonged latency
13	Noguera-Pons ⁶	No	OD: 0.7; OS: 0.7	NR	NR	NR	OD: swollen optic disc; OS: blurred borders of optic discs	Reduced with prolonged latency
14	Chung ¹³	No	OD: 20/30	Positive	Abnormal	OD: inferotemporal pericentral scotoma	Normal	NR
15	Chung ¹³	Yes	OD: 1/200	Positive	Abnormal	OD: central scotoma	OD: mild nasal optic disc swelling	NR

EOM, extra-ocular movement; NR, not reported; OD, right eye; OS, left eye; RAPD, relative afferent pupillary defect; VEP, visually evoked potential testing.

*Cataract and synechia prevented accurate RAPD, visual field testing and fundoscopy.

†Findings at ocular ultrasonography.

‡RAPD could not be measured due to the phthisis of the fellow eye.

§Visual field testing was not reliable because of poor compliance.

injury, as well as their as yet unidentified role in promoting particular immune responses that contribute to demyelination.¹⁴

The index patient presented here displayed many of the typical features of acute demyelinating ON. Judging by the temporal proximity of the onset of the visual symptoms and the initiation of infliximab therapy, as well as the improvement of visual field defects without any recurrence after discontinuation of the drug, we assume a causal link.

Our patient had also been taking isoniazid, a drug known to cause ON as a rare side effect,¹⁵ for 8 months when the visual symptoms emerged.

Recently, Noguera-Pons *et al*⁶ reported a patient having bilateral ON with poor visual outcome presumably resulting from concomitant use of etanercept and isoniazid. Although the contribution of isoniazid to the development of ON in our patient remains a possibility, more cases of ON associated with the concomitant use of anti-TNF α agents and isoniazid are required to conclude whether such a combination has an increased potential for the development of ON.

Certainly, given the small number of cases, it is impossible to rule out the possibility that all those reported cases may represent the background incidence of ON in a population receiving more vigilant follow-up. However, in the light of the abundance of data suggesting a pathogenetic relationship between demyelinating disease and the TNF α pathway, it is theoretically conceivable that its blockade could induce or simply unmask an underlying subclinical demyelinating process.

In clinical practice, the significance of ON as a separate clinical entity stems from the fact that acute demyelinating ON

is the initial presenting manifestation in up to 20% of patients and may occur at any point in the course of disease in up to 50% of MS patients.⁵ A question that remains unanswered awaiting further surveillance and follow-up is whether ON developed during treatment with anti-TNF agents follows a similar course and prognosis to that of idiopathic ON, or whether it represents a transient demyelinating attack without further progression to MS.

Considering the rarity of this condition along with the relatively short follow-up of the reported cases, available data are insufficient to extract firm conclusions about the optimal treatment and follow-up of those patients. However, as outlined in fig 1, we suggest that patients being treated with a TNF α antagonist should be closely monitored for the development of ophthalmological or neurological signs and symptoms. If clinical evaluation leads to the diagnosis of ON, discontinuation of the medication and institution of steroid treatment should be a priority.

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Figure 1 Algorithm for the evaluation and follow-up of a patient receiving anti-tumour necrosis factor (TNF) agents for the development of optic neuritis (ON). MS, multiple sclerosis; RAPD, relative afferent pupillary defect; VEP, visually evoked potential testing; MP, methylprednisolone. Available data suggesting the use of pulse MP for this clinical entity are limited to the cases presented here and elsewhere. However, treatment with steroids can be considered in these patients based on the data regarding the beneficial role of steroids in patients with acute demyelinating ON.

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