CASE REPORT

Acute Inflammatory Optic Neuritis Associated with a Self-Taper of Oral Prednisone in a Patient Taking Adalimumab

Abhinav Komandur ^a, Peter MacIntosh^a, and Heather Moss ^b

^aDepartment of Ophthalmology and Visual Sciences, The University of Illinois College of Medicine, Chicago, Illinois, USA; ^bSpencer Center for Vision Research, Stanford University School of Medicine, Palo Alto, California, USA

ABSTRACT

Therapies, such as adalimumab, aimed at inhibiting the pro-inflammatory cytokine “tumour necrosis factor” (TNF) are effective and are frequently used in combination with non-biologic disease-modifying anti-rheumatic drugs to treat rheumatoid arthritis (RA) and other autoimmune diseases. Some reports indicate that, rarely, demyelinating CNS disorders such as optic neuritis can present in association with therapy initiation, whilst others suggest that there is no association between the two. Oral corticosteroids such as prednisone, though similarly effective in the treatment of inflammatory or auto-immune conditions, can be associated with adverse effects upon their discontinuation or tapering. We present a patient who developed an acute inflammatory optic neuropathy shortly after a self-taper of oral prednisone while being treated with adalimumab for RA, and discuss the challenge of deciding whether or not to halt anti-TNF therapy.

ARTICLE HISTORY

Received 27 July 2018
Revised 17 November 2018
Accepted 3 January 2019

KEYWORDS

Demyelination; optic neuritis; adalimumab; tumour necrosis factor; immune reconstitution inflammatory syndrome

Case report

A 66-year-old female with a 22-year history of rheumatoid arthritis (RA), no history of multiple sclerosis (MS), and non-contributory ocular history presented with a one-week history of painless left-eye vision loss to light perception. She denied jaw claudication and scalp tenderness. Her medications included atorvastatin, felodipine, methotrexate, and adalimumab; she received adalimumab every other week for approximately five years, with her last administration two weeks prior. She had discontinued long-standing prednisone (5mg daily) of her own volition about a month prior; she was uncertain of her tapering regimen. She had a left afferent pupillary defect; the rest of the anterior segment exam was normal. Her left optic nerve appeared oedematous, with a small cup-to-disk ratio and no haemorrhages. CBC was normal and her ESR and CRP were 60 mm/h (normal limits 0–29 mm/h) and 0.5 mg/L (normal limits 0–3.0 mg/L), respectively. She was diagnosed with acute anterior optic neuropathy and was prescribed 60 mg of daily oral prednisone. Temporal artery biopsy nine days afterwards was negative for active, treated, or healed

arteritis. Gadolinium-enhanced MRI demonstrated enhancement of the left optic nerve (**Figure 1**); T2-hyperintense non-enhancing lesions were present on the left midbrain and bilateral periventricular areas (**Figure 2**). No previous imaging results were available. This constellation of findings was concerning for demyelination, though lack of pain was atypical. The patient declined lumbar puncture and IV steroids. Her adalimumab was discontinued out of suspicion for drug-induced de-myelination; methotrexate was continued. Oral steroids were tapered to baseline over two weeks.

One month afterwards, left-eye acuity improved to counting-fingers with central scotoma on Goldmann visual field testing. Repeat MRI demonstrated reduction in enhancement of the left optic nerve; her other noted lesions were stable. Two months afterwards, vision remained stable. Three months after onset, repeat MRI indicated almost complete resolution of the optic nerve enhancement. Four months afterwards, left-eye visual acuity improved to 20/60; seven months afterwards, it improved to 20/40 and Goldmann visual fields were normal. MRI showed resolution

Figure 1. T1-weighted MRI with gadolinium demonstrating enhancement of the left optic nerve.

Figure 2. T2-weighted MRI with gadolinium demonstrating hyperintense non-enhancing lesions on the left midbrain and bilateral periventricular areas.

of the left-optic-nerve enhancement by 15 months afterwards. At last follow-up, about six years after presentation, no further improvement in visual acuity was noted, and no further episodes of neurological dysfunction occurred. The patient remained off adalimumab.

Discussion

This case highlights the clinical challenges faced in management of acute optic neuropathies in a patient with multiple potential inciting factors. Our patient presented with an acute anterior optic neuropathy with MRI enhancement of the optic nerve in the setting of adalimumab use, suggestive

of optic neuritis (ON). Corticosteroids are the accepted acute treatment for ON¹; subsequent management typically varies depending on the suspected cause. Though our patient lacked pain with eye movement and denied permission for a diagnostic LP, MRI suggested demyelinating ON as the most likely cause of her symptoms. Due to the association between anti-TNF biologics and ON, it has become common practice for anti-TNF therapy to be discontinued upon signs of demyelination, as was done in this case.

However, our patient's long-standing history of RA raised the possibility that her demyelinating ON was a sign of an undiagnosed demyelinating disorder, such as relapsing-remitting MS. Her

recent self-taper of oral prednisone also raised an immune reconstitution inflammatory syndrome (IRIS) or an “IRIS-like” condition as a potential incitement of her demyelination – discontinuation of immune suppression is a known (rare) cause of IRIS.² Discontinuation of adalimumab could be unhelpful in the case of an underlying demyelinating condition; it would also not be advisable in the setting of an IRIS-like condition, as an association with discontinuation of immunosuppressive biologics has been previously reported.³ Furthermore, the evidence for a causal relationship between anti-TNF biologic use and demyelinating disorders is ambiguous in the first place.

The main support for a causal relationship comes from case reports of temporal association between anti-TNF medication and CNS de-myelination more generally (e.g. Li, Birnbaum, and Goldstein, 2010).⁴ But, drawing conclusions from case reports is challenging. For example, short follow-up periods make it difficult to capture alternative explanations, such as pre-existing MS. Patients with more advanced or more chronic manifestation of auto-immune disease are also more likely to get these medications; these patients may be more susceptible to demyelinating disease at baseline.⁵ Evidence against a causal relationship in the form of more extensive investigations does exist; however, given the rarity of complications such as de-myelination, it may be insufficient to draw firm conclusions.

Case series have found no significant association between anti-TNF medication and demyelination (e.g. Seror et al, 2010).⁶ However, these are commonly unsuited to capture rare events due to small sample sizes and voluntary reporting. Re-challenge could be used to help prove association, but is not advised due to the morbidity associated with a provoked demyelinating event. To our knowledge, no systematic study of discontinuation with re-challenge phenomena is present in the literature.

Systematic reviews utilising pharmacovigilance, clinical trial, or registry data have also found no association of significance between anti-TNF therapy and de-myelination adverse events. Registries predicated on mandatory reporting do not suffer from selection or reporting bias *within the scope of their data collection*, but analytic methodologies can make drawing clinical conclusions difficult.

For example, analyses using a Spanish registry containing all rheumatology patients administered biologic medications since 2001 lacked negative controls, or controls receiving disease-modifying anti-rheumatic drugs.⁷ Analyses of a similar registry from Great Britain compared psoriatic arthritis patients with RA patients and relied upon voluntary survey response.⁸ A similar U.S. analysis also relied upon voluntary survey response, used a non-comprehensive registry, and did not standardise demyelination diagnosis criteria.⁹ Statistical artefacts related to analysis of rare events or the amalgamation paradox may also be at play in these negative studies.¹⁰

The evidence for a causal relationship between anti-TNF medications and ON therefore remains ambiguous. Case reports raise concern for a rare, disabling complication. Larger studies that would alleviate this concern have methodological problems and may be underpowered to detect rare events. A firm clinical conclusion remains elusive; in the case of our patient specifically, her recent self-taper of oral prednisone further complicated the decision to discontinue adalimumab.

In a case such as this, it is challenging to choose the best management option. A careful history, ocular exam, imaging studies, and CSF analysis can provide valuable insight. However, barring the emergence of Level 1 evidence, clinical decision-making in cases such as ours will continue to be in a context of uncertainty.

Declaration of interest

None to disclose.

ORCID

Abhinav Komandur <http://orcid.org/0000-0002-0334-9107>

Heather Moss <http://orcid.org/0000-0003-4373-447X>

References

1. Volpe NJ. The optic neuritis treatment trial: a definitive answer and profound impact with unexpected results. *JAMA Ophthalmol.* 2008;126:996–999.
2. Johnson T, Nath A. Immune reconstitution inflammatory syndrome and the central nervous system. *Curr Opin Neurol.* 2011;24(3):284–290. doi:10.1097/WCO.0b013e328346be57.

3. Lenhard T, Biller A, Mueller W, Metz I, Schonberger J, Wildemann B. Immune reconstitution inflammatory syndrome after withdrawal of natalizumab? *Neurology*. 2010;75:831–833. doi:[10.1212/WNL.0b013e3181f07362](https://doi.org/10.1212/WNL.0b013e3181f07362).
4. Li SY, Birnbaum A, Goldstein D. Optic neuritis associated with adalimumab in the treatment of uveitis. *Ocul Immunol Inflamm*. 2010;18(6):475–481. doi:[10.3109/09273948.2010.495814](https://doi.org/10.3109/09273948.2010.495814).
5. Lin J, Ziring D, Desai S, Kim S, Wong M, Korin Y, Braun J, Reed E, Gjertson D, Singh RR. TNFalpha blockade in human diseases: an overview of efficacy and safety. *Clin Immunol*. 2008;126(1):13–30. doi:[10.1016/j.clim.2007.08.012](https://doi.org/10.1016/j.clim.2007.08.012).
6. Seror R, Richez C, Sordet C, Rist S, Gossec L, Direz G, Houvenagel E, Berthelot JM, Pagnoux C, Dernis E, Melac-Ducamp S, Bouvard B, Asquier C, Martin A, Puechal X, Mariette X; Club Rhumatismes et Inflammation Section of the SFR. Pattern of demyelination occurring during anti-TNFa therapy: a French national survey. *Rheumatology*. 2013;52:868–874. doi:[10.1093/rheumatology/kes375](https://doi.org/10.1093/rheumatology/kes375).
7. Fernandez-Espartero MC, Perez-Zafrilla B, Naranjo A, et al. Demyelinating disease in patients treated with TNF antagonists in rheumatology: data from BIOBADASER, a pharmacovigilance database, and a systematic review. *Semin Arthritis Rheum*. 2011;41:524–533. doi:[10.1016/j.semarthrit.2011.05.003](https://doi.org/10.1016/j.semarthrit.2011.05.003).
8. Saad AA, Ashcroft DM, Watson KD, Symmons DPM, Noyce PR, Hyrich KL. Efficacy and safety of anti-TNF therapies in psoriatic arthritis: an observational study from the British Society for Rheumatology Biologics register. *Rheumatology*. 2010;49:697–705. doi:[10.1093/rheumatology/kep423](https://doi.org/10.1093/rheumatology/kep423).
9. Gibofsky A, Palmer WR, Keystone EC, Schiff MH, Feng J, McCroskery P, Baumgartner SW, Markenson JA. Rheumatoid arthritis disease-modifying antirheumatic drug intervention and utilization study: safety and etanercept utilization analyses from the RADIUS 1 and RADIUS 2 registries. *J Rheumatol*. 2011;38:21–28. doi:[10.3899/jrheum.100347](https://doi.org/10.3899/jrheum.100347).
10. Leombruno J, Einarson T, Keystone E. The safety of anti-tumour necrosis factor treatments in rheumatoid arthritis: meta and exposure-adjusted pooled analyses of serious adverse events. *Ann Rheumatic Dis*. 2009;68:1136–1145. doi:[10.1136/ard.2008.091025](https://doi.org/10.1136/ard.2008.091025).