MSJ Experimental Translational Clinical

Original Research Article

Central Nervous System Demyelination Related to Tumour Necrosis Factor Alpha Inhibitor

Multiple Sclerosis Journal—Experimental, Translational and Clinical

January–March 2022, 1–7

DOI: 10.1177/20552173211070750

Shin Yee Chey and Allan G. Kermode

Abstract

Background: An association between tumour necrosis factor alpha (TNF-α) inhibitors exposure and central nervous system (CNS) demyelinating disorders has been postulated but is poorly understood.

Objectives: Describe the clinical spectrum and progress of a cohort of patients who developed demyelinating disorder following exposure to TNF-α inhibitor.

Methods: Retrospective chart review of patients who presented to a single neurologist in Western Australia between May 2003 and July 2020.

Results: 7 patients (6 females and 1 male) were identified. Mean age was 49.1 years. Mean follow-up time was 2.9 years. Mean interval between commencement of TNF-α inhibitor and onset of demyelinating event was 3 years. The spectrum of demyelinating events included transverse myelitis ($N = 3$), acute brainstem syndrome ($N = 1$) and optic neuritis ($N = 1$). 2 patients had an atypical presentation but had MRI findings which unequivocally showed demyelinating changes. 2 patients had a monophasic event while the other 5 patients were diagnosed to have multiple sclerosis. All symptomatic patients with multiple sclerosis were started on disease modifying therapy and remained relapse free during follow-up.

Conclusion: Exposure to TNF-α inhibitor appears to increase the risk of demyelinating event. Whether TNFα inhibition directly results in CNS demyelination or trigger demyelination in susceptible individuals requires further research.

Keywords: demyelinating disorders, tumour necrosis factor alpha inhibitor, multiple sclerosis, transverse myelitis, optic neuritis, central nervous system inflammation

Date received: 22 June 2021; accepted: 15 December 2021

Introduction

TNF-α is a pro-inflammatory cytokine which plays a crucial role in various immune-mediated conditions including inflammatory bowel disease and rheumatological disorders such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Five TNF-α inhibitors, namely etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol have been approved for the treatment of these diseases. Although proven to be efficacious, there have been reports on the association of TNF-α inhibitors with CNS demyelination.[1,2] Although a causal relationship between TNF-α inhibition and demyelinating disease remains uncertain, it is extremely important to recognise this as a complication. In this series, we present a cohort of 7 patients who developed demyelinating disorder following exposure to TNF-α inhibitor and describe the clinical spectrum as well as progress of these patients.

Materials and methods

Patients who developed one or more demyelinating event following the administration of anti-TNFα between May 2003 and July 2020 were identified retrospectively from a single neurologist in Western Australia. Demographic data, clinical characteristics, laboratory results, neuroimaging and clinical progress were reviewed. The diagnosis of multiple sclerosis (MS) was made by AGK according to the revised McDonald criteria in 2017. Written informed consent was obtained from all patients.

Correspondence to:
Shin Yee Chey,
Department of Neurology, Sir Charles Gairdner Hospital, Hospital Ave, Nedlands Western Australia, 6009 Australia.
shin.yee@live.com

Shin Yee Chey,
Department of Neurology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia
Perron Institute for Neurological and Translational Sciences, Perth, Australia

Allan G. Kermode,
Perron Institute for Neurological and Translational Sciences, Perth, Australia

Results

Table 1 demonstrates the demographic, clinical and radiological data for all patients.

Study cohort and baseline characteristics

Table 2 shows a summary of demographic data for all patients. A total of 7 patients were identified and this comprised of 6 females and one male. The mean age of onset of the first demyelinating event was 49.1 years. 6 patients were Caucasians and 1 patient was of Vietnamese descent and migrated to Australia 28 years previously. 2 patients were treated for PsA, 1 for RA, 1 for AS, 1 for seronegative inflammatory arthropathy, 1 for Adult-onset Still's Disease and 1 for Crohn's disease (CD). Only one patient (Patient 7) had family history of demyelination in a first degree relative. One patient (Patient 3) had strong family history of autoimmune disease (Hashimoto's thyroiditis and systemic lupus erythematosus (SLE) in two first degree relatives). One patient had concomitant Hashimoto's thyroiditis. The mean follow-up time was 2.9 years.

Anti-TNFα exposure

4 patients received more than one successive treatment of TNFα inhibitors, with 2 of the patients developing symptoms soon after switching over to a different TNFα inhibitor. 3 patients were exposed to infliximab, 5 to adalimumab, 2 to golimumab and 1 to certolizumab. The mean interval between commencement of TNF-α inhibitor and development of the first demyelinating event was 3 years (obtained only from 4 patients as this information was uncertain for patients 1, 3 and 7).

Clinical presentation

3 patients presented with transverse myelitis, 1 had acute brainstem syndrome and 1 developed optic neuritis. 2 patients had atypical presentations but had MRI findings which unequivocally showed changes consistent with demyelination. One of these patients (Patient 3) presented with a radiologically isolated syndrome discovered after a syncopal event, with her initial cranial MRI demonstrating several asymptomatic lesions including a lesion with open ring enhancement. Another patient (Patient 7) presented with psychiatric symptoms a few years after ceasing TNFα inhibitor, and was subsequently found to have demyelinating changes on MRI Brain. Patient 4 had a history of optic neuritis 9 years prior to anti-TNFα therapy but developed a recurrent episode of optic neuritis while she was receiving TNF-α inhibitor therapy. Figure 1 shows representative cranial and spinal MRI images of patients 2 to 7.

Treatment and progression

TNF-α inhibitor was ceased in all patients. 2 patients had a monophasic demyelinating event while 5 patients (patients 2,3,4,5 and 7) were eventually diagnosed to have MS. Patients 4 and 5 satisfied the 2017 McDonald criteria at the time of presentation. Patient 2 developed a new periventricular lesion during follow-up after three prior clinical events, two of which were associated with relevant MRI changes at the levels of C2 and T9 of the spinal cord (Figure 1A). Patient 3 did not fulfil the diagnosis of MS initially, but developed clumsiness of her left hand during follow-up, with her repeat cranial MRI performed 5 months after cessation of anti-TNFα therapy showing a new lesion, and hence fulfilling the diagnosis of MS (Figure 1B). Another patient (Patient 7) had MRI brain and spine which satisfied criteria for MS, but remained largely asymptomatic without new radiological changes over 6 months following the cessation of anti-TNFα (Figure 1F). MS immunotherapy has not been commenced and the patient continues with close clinical and MRI monitoring. He has however been started on Tocilizumab for seronegative inflammatory arthritis. The remaining 4 patients who were diagnosed with MS received disease modifying therapy (DMT), with 2 receiving natalizumab, 1 receiving fingolimod and 1 receiving ocrelizumab. All patients who received DMT remained relapse free during follow-up.

Discussion

We speculate that the CNS demyelinating events in our case series may be associated with exposure to anti-TNFα therapy. There have been reports which suggest a link between TNF-α blockers and CNS inflammatory demyelinating disease.[3] Earlier evidence includes a phase II placebo-controlled trial which was originally conducted to evaluate lenercept, a TNF-α inhibitor as a potential treatment for MS which demonstrated paradoxical worsening in MS patients who received lenercept.[4] This is further substantiated by a recent case-controlled study which showed an increased risk of inflammatory demyelinating disorders in patients who received TNF-α inhibitor.[5]

It remains unclear as to whether TNF-α inhibition directly results in CNS demyelination or only triggers demyelination in genetically predisposed individuals such as patient 7 who has positive family history of demyelination. In addition, patient 4 had a prior

Table 1. Demographic, clinical and radiological data of the patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Age of onset/Sex	63/F	41/F	36/F	49/F	30/F	65/F	60/M
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Vietnamese	Caucasian
Family History	No	No	No*	No	No	No	Yes***
Indication of anti-TNFα	RA	AS	PsA	PsA	CD	Seronegative inflammatory arthropathy	Adult Still's disease
Comorbidity	No	Obesity	IIH,DVT	Hashimoto's thyroiditis, PCOS, obesity	No	Chronic Hepatitis B, DM, HTN, OSA, hyperlipidaemia	DM with nephropathy, HTN, dyslipidaemia, ADHD
Anti-TNFα	IFX	ADA (1y) followed by IFX	GOL (a few years), followed by ADA	GOL	ADA (3y) followed by IFX	ADA(2y) followed by CTZ	ADA
Interval between anti-TNFα initiation and demyelination	NA	1 y	Symptom developed shortly after the first dose of ADA	7y	2y	2y (symptom developed immediately after first CTZ infusion)	NA
Clinical characteristic	TM	Recurrent TM	-	ON**	Recurrent TM	Acute brainstem syndrome	-
Symptoms	Paraesthesia below T8/9 level and perianal region, urinary disturbance	3 clinical events involving left lower limb weakness, right arm incoordination, Lhermitte's phenomenon	Syncope, left hand clumsiness and loss of facility	Inferior altitudinal field defect, pain on eye movement	3 clinical episodes with paresthesia waist down and left upper limb, bladder disturbance	Paraesthesia of the face and tongue, unsteady gait	Psychiatric symptoms
MRI findings	Hyperintensities T8/9 with asymmetry more on the left than right (Gd-)	Short segment hyperintensiti-es lateral cord at C2 and T9 (Gd-)	Multiple lesions periventricular, corpus callosum, one lesion occipital horn of right lateral ventricle with open ring appearance (Gd+)	Multiple periventricular and subcortical white matter lesions including one left temporal. Hyperintensity left pons (Gd-)	Multiple lesions involving juxtacortical, periventricular (1 Gd+lesion left corona radiata). Multiple short segment dorsal/ lateral cord lesions at C5, C6/ C7, T5, T8/9, T10 (Gd-)	Midbrain T2 hyperintensity centrally, posterior to the interpeduncular notch. (Gd-)	Left frontoparietal juxtacortical lesion, multiple periventricular lesions (radial configuration and perivenular distribution), increased signal left optic nerve, lesion in left brachial pontis,

(continued)

Table 1. Continued.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
							pons, pontomedullary junction (Gd-), cord lesions at C5 and T12(Gd-)
Relevant laboratory findings	CSF OCB Negative	-	-	-	-	CSF OCB & serum AQP4 Negative	-
Duration of follow-up	6y	4y5m	4y	4y1m	4m	5m	9m
Progression/ Outcome	Monophasic demyelinating event. Serial MRI no interval changes	MS – developed a new periventricular lesion. No further relapse since DMT started	MS – developed a new ovoid lesion right posterior frontal region and another lesion periventricular white matter of the left temporal lobe 5 m following cessation of anti-TNF-α. No further relapse since DMT started	MS- No further relapse since DMT started	MS- No further relapse since DMT started	Monophasic demyelinating event. Serial MRI unchanged.	MS- No clinical and radiological progression
Cessation of anti-TNFα	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Treatment	Steroid during acute presentation. No DMT	Fingolimod, Secukinumab (for refractory PsA)	Leflunomide (ceased following severe GI side effects), Ocrelizumab	Initial steroid for ON followed by Natalizumab	Natalizumab	NIL	Tocilizumab for seronegative inflammatory arthritis. No DMT

Legend: RA: Rheumatoid arthritis, PsA: psoriatic arthropathy, AS: ankylosing spondylitis, CD: Crohn's disease, anti-TNF-α: Tumour necrosis factor alpha antagonist, ADA: Adalimumab, GOL: Golimumab, IFX: Infliximab, CTZ: Certolizumab, m: month, y: year, F: Female, M: Male, ON: Optic neuritis, TM: Transverse myelitis, DM: Diabetes mellitus, HTN: Hypertension, IIH: Idiopathic intracranial hypertension, DVT: deep vein thrombosis, PCOS: Polycystic ovarian syndrome, OSA: obstructive sleep apnoea, ADHD: Attention deficit hyperactive disorder, AQP4: Aquaporin 4 antibody, DMT: Disease modifying therapy, NA: not available, MRI: magnetic resonance imaging, OCB: oligoclonal bands, GI: gastrointestinal, MS: multiple sclerosis, Gd+: gadolinium enhancement, and Gd-: no gadolinium enhancement.

*Mother has Hashimoto's thyroiditis and systemic lupus erythematosus, brother has Hashimoto's thyroiditis.

**patient had history of left optic neuritis 9 years prior to anti-TNFα therapy with some MRI brain changes which did not fulfil criteria for MS, but developed a second episode of optic neuritis while on TNF-α inhibitor.

***patient's sister has demyelinating disease.

Table 2. Summary of demographic data and clinical information of patients.

		Frequency
Total number of patients		7
Age		49.1 years
Gender	Female	6
	Male	1
Ethnicity	Caucasian	6
	Asian	1
Mean follow up		2.9 years
Positive family history of demyelinating disease		1
Diagnosis	RA	1
	PsA	2
	AS	1
	IBD	1
	Adult-onset Still's Disease	1
	Seronegative inflammatory arthropathy	1
TNF-αInhibitor (Frequency of exposure)	Infliximab	3
	Adalimumab	5
	Golimumab	2
	Certolizumab	1
Mean interval between commencement of anti-TNFα and onset of first demyelinating event		3 years (Mean obtained from 4 patients due to uncertain information from patients 1, 3 and 7)

history of optic neuritis with abnormal baseline MRI Brain which predated TNF-α inhibitor exposure, and this may indicate susceptibility to CNS demyelination. It may be possible that introduction of TNF-α inhibitor in these individuals merely unmasked or precipitated the demyelinating disorders.

Two previous studies found that the mean interval between initiation of TNF-α and onset of demyelination were 5 months and 17.6 months respectively.[1,2] The time interval in our patients was 3 years which is much longer than previously described. Interestingly, patients 3 and 6 who received more than one successive anti-TNF-α appeared to tolerate the first TNFα inhibitor but developed symptoms soon after being switched to a different TNFα inhibitor. The reason for this observation is unclear, and to our knowledge, this observation has not been reported previously. It may be possible that these TNFα inhibitors have a subtle difference in side effect profiles, analogous to how some patients respond well to one anti-TNF-α but not to the other due to the underlying structural and immunological differences.[6,7]

We also found that cessation of TNF-α blockers does not always lead to resolution. Patient 3 developed a new brain lesion on MRI 5 months later despite cessation of the drug. A previous study showed that a small group of patients developed MS after a mean follow-up of only 20.4 months.[3] Hence, patients who do not initially fulfil criteria for MS need to be monitored for further demyelinating events despite stopping TNF-α inhibitor.

There are no specific guidelines on management of patients who develop a demyelinating event during TNF-α inhibitor therapy. Cessation of TNF-α inhibitor is of the utmost importance. In our cohort, all appropriate patients who fulfilled the diagnosis of MS were started on a DMT. There is no consensus on the choice of DMT in patients with concomitant rheumatological disorders.

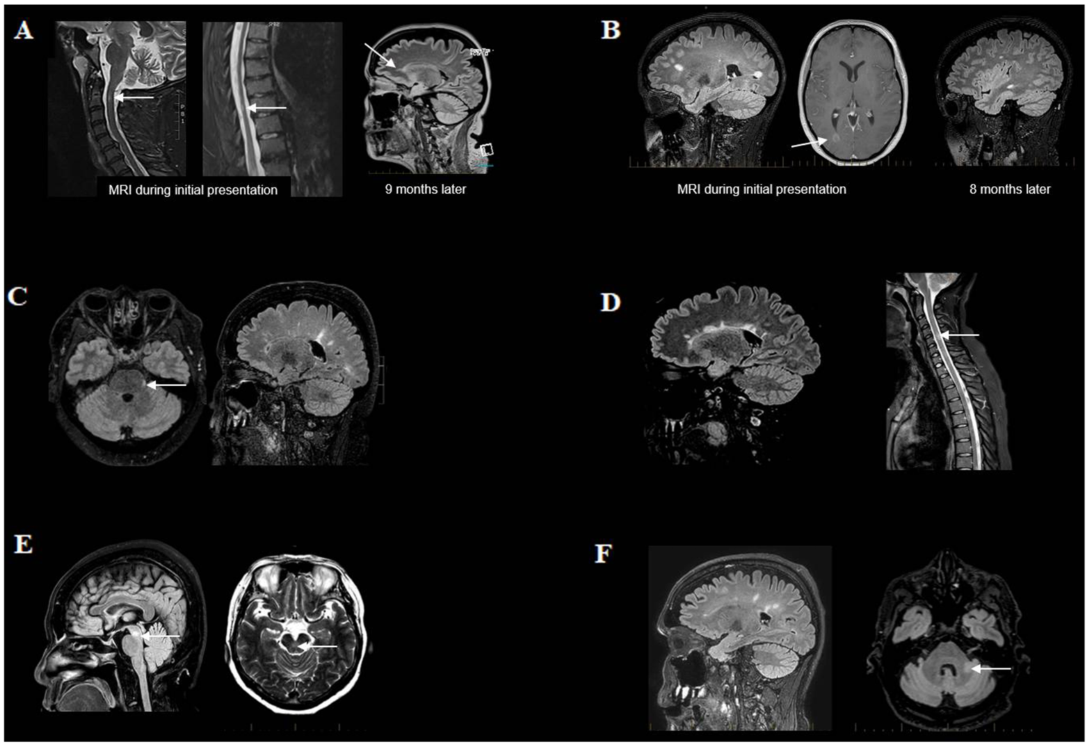

Figure 1. Representative cranial and spinal MRI images of patients 2 to 7. **(A)** Patient 2 with T2-weighted sagittal image showing an area of hyperintensity at the level of C2 and T9 of the spinal cord. The third image is a sagittal FLAIR sequence showing a new linear focus of periventricular hyperintensity anterior to the frontal horn of right lateral ventricle. **(B)** Patient 3 with FLAIR image showing a lesion over the right frontal periventricular white matter and another lesion in the occipital horn of right lateral ventricle. The second image demonstrates an open ring enhancement of the lesion in the occipital horn of the right lateral ventricle. The third image from the left demonstrates a single new lesion in the periventricular white matter of the left temporal lobe which developed 8 months later. **(C)** Patient 4 with FLAIR image showing periventricular white matter lesions and a lesion in the pons near the root entry zone of the trigeminal nerve on the left **(D)** Patient 5 with FLAIR study showing multiple pericallosal lesions and STIR sequence showing a short segment cord lesion at the level of C5 of the cord **(E)** Patient 6 with sagittal FLAIR and T2-weighted axial studies demonstrating a poorly defined lesion in the midbrain at the level of interpeduncular notch **(F)** Patient 7 with sagittal FLAIR image showing periventricular white matter lesions and a lesion in the left brachium pontis.

Ocrelizumab, a humanized anti-CD20 monoclonal antibody has been shown to be efficacious and safe in patients with RA.[8] In addition, there have been reports on successful use of rituximab, another anti-CD20 monoclonal antibody in a small group of patients with PsA.[9,10] Therefore, ocrelizumab seemed to be a reasonable option for patient 3 who has PsA. On the other hand, natalizumab, a humanised monoclonal antibody directed against alpha-4 integrin has been shown to be beneficial for treating Crohn's disease[11,12] and thus became the treatment option for patient 7.

Although the presence of oligoclonal bands in patients with first demyelinating events has been demonstrated to increase the risk of MS,[13] it is unclear how this would relate to anti-TNFα therapy. In this clinical context, the pragmatic approach is one of close clinical observation, MRI follow-up for asymptomatic change, and avoidance of current and future TNFα blockade.

Conclusion

Exposure to TNFα inhibitor appears to increase the risk of demyelinating events. Whether TNF-α inhibition directly results in CNS demyelination or triggers demyelination in susceptible individuals requires further research.

Healthcare professionals should be aware of the risks using TNF-α inhibitors especially in high-risk cases such as patients with family history of demyelination or a prior demyelinating event.

It is important to have a high index of suspicion in those who develop neurological symptoms following administration of TNF-α inhibitor. Cessation of anti-TNFα therapy is required, but this may not necessarily lead to a self-limiting disease course. Patients will require close monitoring for further events even after the cessation of anti-TNFα therapy.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Shin Yee Chey has no disclosures. Allan Kermode has in recent times received speaker honoraria and Scientific Advisory Board fees from Bayer, BioCSL, Biogen-Idec, Merck, Novartis, Roche, Sanofi-Aventis, Sanofi-Genzyme, Teva, NeuroScientific Biopharmaceuticals, Innate Immunotherapeutics, and Mitsubishi Tanabe Pharma.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

ORCID iDs

Shin Yee Chey https://orcid.org/0000-0003-2192-0941
Allan G. Kermode https://orcid.org/0000-0002-4476-4016

References

1. Mohan N, Edwards ET, Cupps TR, et al. Demyelination occurring during anti-tumor necrosis factor α therapy for inflammatory arthritides. *Arthritis Rheum* 2001; 44: 2862–2869.
2. Andreadou E, Kemanetzoglou E, Sfakianaki K, et al. Demyelinating disease following anti-TNF-alpha treatment. A causal or coincidental association? Report of two cases. *Eur J Neurol* 2012; 19: 714. http://bf4dv7zn3u.search.serialssolutions.com.myaccess.library.utoronto.ca/?url_ver=Z39.88-2004&rft_val_fmt=info:ofi/fmt:kev:mtx:journal&rfr_id=info:sid/Ovid:emed10&rft.genre=article&rft_id=info:doi/10.1111%2Fj.1468-1331.2012.03889.x&rft_id=info:pmid/&rft.
3. Kemanetzoglou E and Andreadou E. CNS Demyelination with TNF-α blockers. *Curr Neurol Neurosci Rep* 2017; 17(4): 36.
4. Arnason BGW. TNF Neutralization in MS: results of a randomized, placebo-controlled multicenter study. *Neurology* 1999; 53: 457–465.
5. Kunchok A, Aksamit AJ, Davis JM, et al. Association between tumor necrosis factor inhibitor exposure and inflammatory central nervous system events. *JAMA Neurol* 2020; 77: 937–946.
6. Van Vollenhoven R, Harju A, Brannemark S, et al. Treatment with infliximab (Remicade) when etanercept (Enbrel) has failed or vice versa: data from the STURE registry showing that switching tumour necrosis factor α blockers can make sense. *Ann Rheum Dis* 2003; 62: 1195–1198.
7. Mpofu S, Fatima F and Moots RJ. Anti-TNF-α therapies: they are all the same (aren't they?) *Rheumatology* 2005; 44: 271–273.
8. Abushouk AI, Ahmed H, Ismail A, et al. Safety and efficacy of ocrelizumab in rheumatoid arthritis patients with an inadequate response to methotrexate or tumor necrosis factor inhibitors: a systematic review and meta-analysis. *Rheumatol Int* 2017; 37: 1053–1064.
9. Cohen JD. Successful treatment of psoriatic arthritis with rituximab. *Ann Rheum Dis* 2008; 67: 1647–1648.
10. Wendling D, Dougados M, Berenbaum F, et al. Rituximab treatment for spondyloarthritis. A nationwide series: data from the AIR registry of the French society of rheumatology. *J Rheumatol* 2012; 39: 2327–2331.
11. Sandborn WJ, Colombel JF, Enns R, et al. Natalizumab induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2005; 353: 1912–1925.
12. Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol* 2011; 106: 644–659.
13. Tintoré M, Rovira A, Río J, et al. Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? *Neurology* 2008; 70: 1079–1083.