Central Nervous System Demyelination Related to Tumour Necrosis Factor Alpha Inhibitor

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 TNF-α 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.

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**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. Earlier evidence includes a phase II placebo-controlled trial which was originally conducted to evaluate lenenercept, a TNF-α inhibitor as a potential treatment for MS which demonstrated paradoxical worsening in MS patients who received lenenercept. 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.

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
| 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 | Yes | No |
| Indication of anti-TNFα | RA | AS | PsA | PsA | CD | ** | 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, dyshlipidaemia, ADHD, ADA, MI |
| 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 | NA |
| Interval between anti-TNFα initiation and demyelination | NA | 1 y | Symptom developed shortly after the first dose of ADA | 7y | 2y | 2y | NA |
| Clinical characteristic Symptoms | TM | Recurrent TM | - | ON** | Recurrent TM | Acute brainstem syndrome | - |
| MRI findings | 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 | Paresthesia 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 hyperintensities lateral cord at C2 and T9 (Gd-) | Multiple lesions periventricular, corpus callosum, one lesion occipital hom 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 periventricular distribution), increased signal left optic nerve, lesion in left brachial pontis, (continued) |
| 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 Treatment | 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, GE: 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.
history of optic neuritis with abnormal baseline MRI brain which predated TNF-\(\alpha\) inhibitor exposure, and this may indicate susceptibility to CNS demyelination. It may be possible that introduction of TNF-\(\alpha\) inhibitor in these individuals merely unmasked or precipitated the demyelinating disorders.

Two previous studies found that the mean interval between initiation of TNF-\(\alpha\) 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-\(\alpha\) appeared to tolerate the first TNF\(\alpha\) inhibitor but developed symptoms soon after being switched to a different TNF\(\alpha\) 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 TNF\(\alpha\) inhibitors have a subtle difference in side effect profiles, analogous to how some patients respond well to one anti-TNF-\(\alpha\) but not to the other due to the underlying structural and immunological differences.\(^5,7\)

We also found that cessation of TNF-\(\alpha\) 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-\(\alpha\) inhibitor.

There are no specific guidelines on management of patients who develop a demyelinating event during TNF-\(\alpha\) inhibitor therapy. Cessation of TNF-\(\alpha\) 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.

| Table 2. Summary of demographic data and clinical information of patients. |
|----------------------------------|----------------|
| 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 arthropyathy 1 |
| TNF-\(\alpha\)Inhibitor (Frequency of exposure) | Inflimixab 3, Adalimumab 5, Golimumab 2, Certolizumab 1 |
| Mean interval between commencement of anti-TNF\(\alpha\) and onset of first demyelinating event | 3 years (Mean obtained from 4 patients due to uncertain information from patients 1, 3 and 7) |
Ocrelizumab, a humanized anti-CD20 monoclonal antibody has been shown to be efficacious and safe in patients with RA. In addition, there have been reports on successful use of rituximab, another anti-CD20 monoclonal antibody in a small group of patients with PsA. Therefore, ocrelizumab seemed to be a reasonable option for patient 3 who has PsA. On the other hand, natalizumab, a humanized monoclonal antibody directed against alpha-4 integrin has been shown to be beneficial for treating Crohn’s disease 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, 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

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**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.
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.

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