

# Tumor necrosis factor-alpha antagonist and demyelinating diseases

J. Balsalobre Aznar, J. Porta-Etessam, J. Salvatierra Ossorio, J.L. Rosales-Alexander

\*Corresponding author:

✉ [jporta@yahoo.com](mailto:jporta@yahoo.com)

## Abstract

Anti-TNF treatment –associated disorders have emerged as a new class of drug-related demyelinating neurological disease. Neurological deficits that develop during treatment with TNF-alfa antagonists are relatively rare (the prevalence of demyelinating disease, as reported in randomized controlled trials and postmarketing studies, has been estimated to range from 0,02-0,2%) but important potential complications of these drugs. Most of the patients described in the literature had no personal or family history of Multiple Sclerosis. These disorders include, among others, multiple sclerosis, optic neuritis, and various forms of peripheral demyelinating neuropathy. Short-term follow-up indicates relatively good outcomes, sometimes after just treatment discontinuation, although corticosteroids or intravenous immunoglobulin may be necessary to reverse and stabilize these disorders. Definitive cessation of the biological therapy should be discussed on a case-by-case basis

**Keywords:** TNF-alpha, demyelinating diseases, multiple sclerosis, optic neuritis.



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## Introduction

Inhibitors of tumor necrosis factor-alpha (TNF-alpha) represent important treatment advances in a considerable number of inflammatory conditions, offering a targeted strategy that contrasts with the non-specific immunosuppressive agents traditionally used to treat most inflammatory diseases until recently.

However, multiple adverse effects of TNF inhibition have been identified through both clinical trials and post-marketing surveillance. These later include demyelinating disease (DD) including Multiple Sclerosis (MS).

Before applying results of a study to a patient, one must consider the possible harm that any intervention might do. Regardless of this crucial information, reporting of harms in randomized controlled trials has received less attention than reporting of efficacy and is often inadequate. Looking at the rate of adverse effects reported in each group helps in appraising the risks of a treatment.

Up to now, long-term clinical studies assessing the safety of anti-TNF- $\alpha$  drugs have failed to show a higher rate of neurological disorders in treated patients than in the general population([5, 9, 11 ]. However, studies are never powered to detect a statistically significant difference in rates between groups. Sample sizes are usually too small for a reasonable chance of detecting an unexpected adverse effect. This seems to be the case of DD related to the use of TNF blockers.

Assessing the likelihood of a causal connection between an environmental exposure -a drug, in this case-, the five primary elements of attribution reported by Miller [15], include 1, temporal association; 2, lack of likely alternative explanations; 3, dechallenge; 4, rechallenge and 5, biological plausibility. All of them have been observed in the DD related to anti-TNF blockers which have been described in the literature.

A recent analysis of 151 reported cases of DD CNS processes after the starting of TNF blockers included mainly optic neuritis (ON) (80% of the patients) but also MS/MS-like disorders and myelitis [1].

Solomon et al. [2] describe 151 cases which summarize 64 cases of CNS syndromes, 18 cases of isolated optic neuritis, and 69 cases of neuromuscular syndromes. The majority of reported cases included females (66.2%) suffering from rheumatoid arthritis (50.3%).

Most (84%) of CNS cases began after the age of 36, which differs from a reference point of 25-35 years as being the typical peak incidence of MS.

Neurological symptom onset occurred within one year of beginning TNF-alpha inhibitor therapy in 72% of CNS cases, 88% of optic neuritis cases, and 81% of neuromuscular cases.

Etanercept (Enbrel®) therapy was reported in the majority of cases of CNS syndromes (62%) and infliximab (Remicade®) therapy in the majority of optic neuritis (65%) and neuromuscular syndromes (67%). The smaller number of cases involving adalimumab (Humira®) may reflect more recent approval by the FDA rather than a decreased risk associated with this treatment choice.

Clinical outcomes reported at follow-up in 56 CNS cases include: Complete resolution of symptoms (25%), partial improvement (44.6%), unchanged or stable symptoms (12.5%), a relapsing-remitting course after initial presentation (16%), and one progressive disease course (0.02%). Clinical outcomes reported in 17 optic neuritis cases include: complete resolution (35.3%), partial improvement (47.8%) and unchanged or stable symptoms (23.5%). Clinical outcomes reported in 68 neuromuscular cases include: Complete resolution (36.8%), partial improvement (45.6%), unchanged or stable symptoms (7.4%), and a relapsing-remitting course (10.3%).

The majority of reports (67.4%) detailed significant disability at the time of follow-up. However, most cases (82%) had been followed for less than one year after onset of neurological disease.

Longer follow-up could reveal the emergence of a relapsing-remitting syndrome or a later full recovery without recurrence. More detailed study is needed in future cases to better determine the natural course of the disease development and to evaluate appropriate treatment interventions.

In a French national survey [3], 33 patients were identified; although all patients discontinued the treatment 5 developed MS. Two patients have relapsed after the introduction of another anti TNF.

## The precedent

Concern regarding demyelination or the exacerbation of intercurrent DD in patients treated with these agents stem from the use of a TNF-alpha receptor p-55 immunoglobulin fusion protein, lenercept, in multiple sclerosis (MS). Lenercept was halted in clinical trials because it produced more frequent and severe exacerbations of MS than those who received placebo. Most patients had relapsing-remitting disease. The code was broken once all patients had been treated for at least 24 weeks. Patients on the drug experienced one and a half times as many MS attacks as those on placebo. MS attacks lasted one and a half times as long in those on the drug as those on placebo. Additionally, MS-related complaints voiced by patients on drug were much increased [4].

## The explanation

TNF $\alpha$  is a cytokine secreted by T-cells and macrophages that is an important component in the immune-mediation of demyelination. In vivo and in vitro experiments have suggested a correlative relationship between elevated TNF $\alpha$  and the severity of DD [5]. The effect of TNF inhibition was investigated in murine experimental autoimmune encephalitis (EAE) and the initial results were promising [6, 7, 8, 9]. However, neutralization of TNF $\alpha$  in humans did not result in an improvement in DD in MS, but rather it seemed to exacerbate it [10, 11]. Several explanations of its failure in humans include the inability of the TNF $\alpha$  inhibitor to penetrate the blood brain barrier and the complex role that TNF $\alpha$  plays in remyelination and regulation of other cytokines and lymphocytes. Several theories have been put forth to explain this relation [5, 9], such as local immune dysregulation by TNF- $\alpha$  blockage leading to prolonged survival of myelin-specific activated T cells and increased cytokine production, vasculitis-induced ischemia and altered repairing of axonal injuries, and myelin damage by TNFR2 inhibition. Tumor necrosis factor alpha (TNF- $\alpha$ ) is a cytokine with pleiotropic actions that can be present both as a transmembrane protein and soluble cytokine (sTNF). Both ligands interact with two different receptors, TNFR1 and TNFR2, which mediate their biological effects. Inasmuch as TNFR1 mediates demyelination and TNFR2 remyelination, it could be hypothesized that anti-TNF- $\alpha$  agents which selectively inhibit sTNF or signals from TNFR1 could be effective in treating MS [16].

## Optic Neuritis (ON)

ON is an inflammatory, DD that causes acute, usually monocular, visual loss. Vision loss typically develops over a period of hours to days, peaking within one to two weeks. The visual field defect in ON is typically characterized as a central scotoma. However, almost all types of visual field defects can be seen. Eye pain occurs in almost all patients and is often worsened with eye movement. An afferent pupillary defect always occurs in ON. This is demonstrated by shining a light alternately in one eye and then the other and finding that the direct response to light is more sluggish in the affected eye. Papillitis with hyperemia and swelling of the disk, blurring of disk margins, and distended veins is seen in one-third of patients with ON. Two-thirds of these patients have retrobulbar neuritis with a normal funduscopy examination ON related to anti-TNFblockers are predominantly retrobulbar [3]. The reported prevalence of white matter abnormalities on MRI varies substantially among patients with ON (23 to 75 percent). In general, optic neuritis is a clinical diagnosis based upon the history and examination findings [17].

A review of the Adverse Events Reporting System database of the Food and Drug Administration in 2001 identified 20 cases of DD following treatment with anti TNF $\alpha$  agents for arthritis. ON was reported to be the second most common presentation (8 of), and it was the sole presenting symptom among two of them [18]. Chung et al. [18] first described two cases of adalimumab associated optic neuritis. Subsequently, Simsek et al [19] reviewed 15 cases of all TNF $\alpha$  antagonist associated ON in the literature. The interval from the initial administration to presentation ranged from 2 months to 1.5 years (median 7.5 months). All but one were treated with pulse steroids (GC) followed by oral GC. Nine of the 15 patients had a complete visual recovery. Of the eight patients who had a brain MRI reported, only two had findings suggestive of demyelination. Interestingly, after 4 to 6 months, the two with significant MRI findings had only partial visual.

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 MS patients and may occur at any point in the course of disease in up to 50% of MS patients([1 ]. 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.

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. Supporting this hypothesis, Winthrop et al [20] in a retrospective, population-based cohort study analysed 61; 227 inflammatory disease patients with either new anti-TNF or new non-biologic disease modifying drugs (DMARD) use. Six ON cases -3 among anti-TNF users and 3 among DMARD users- were identified. Crude ON rates were similar among anti-TNF and DMARD groups: 4.5 (95% CI 1.4-13.8) and 5.4 (95% CI 1.7-16.6) per 100 000 person-years, respectively. The authors conclude that ON is rare among those who initiate anti-TNF therapy and occurs with similar frequency among those with non-biologic DMARD exposure. However, in the light of the abundance of data suggesting a pathogenetic relationship between demyelinating disease and the TNF $\alpha$  pathway, it is theoretically conceivable that its blockade could induce or simply unmask an underlying subclinical DD.

Involvement of the nerve fibers in the optic chiasm (chiasmopathy) has also been rarely described. This case is of special interest because the involvement of the anterior visual pathways was in the optic chiasm, as manifested by the bitemporal hemianopic scotomas. While previously reported cases involved the optic nerves, the same nerve fibers that are in the optic nerves pass through the chiasm. Indeed, bitemporal visual field defects have been reported in cases of presumed multiple sclerosis. This patient did not need GC treatment, just discontinuation of the anti-TNF blocker [21].

## Guillain-barre and Miller Fisher syndrome.

Most often, Guillain-Barré (GBS) presents as an acute monophasic paralyzing illness provoked by a preceding infection. The cardinal clinical features of GBS are progressive, fairly symmetric muscle weakness accompanied by absent or depressed deep tendon reflexes. Patients usually present a few days to a week after onset of symptoms. The weakness can vary from mild difficulty with walking to nearly complete paralysis of all extremity, facial, respiratory, and bulbar muscles. GBS usually progresses over a period of about two weeks. By four weeks after the initial symptoms, 90 percent of GBS patients have reached the nadir of the disease [22]. The typical finding with lumbar puncture in patients with GBS is an elevated cerebrospinal fluid (CSF) protein with a normal white blood cell (WBC) count. Clinical neurophysiology studies (ie., electromyography and nerve conduction studies) show evidence of an acute polyneuropathy with predominantly demyelinating features in acute inflammatory demyelinating polyradiculoneuropathy (AIDP), while the features are predominantly axonal in acute motor axonal neuropathy (AMAN) and acute sensorimotor axonal neuropathy (AMSAN) [23].

The typical presentation of Miller-Fisher Syndrome (MFS) is that of ophthalmoplegia with ataxia and areflexia. About

one-quarter of patients who present with MFS will develop some extremity weakness, clearly linking this disorder to GBS. Clinical neurophysiology studies in patients with MFS reveal reduced or absent sensory responses without slowing of sensory conduction velocities. When there is associated weakness, the motor nerve conduction abnormalities of AIDP may be present [24].

A review of the occurrence and clinical features of GBS and its variant, the MFS, during TNF $\alpha$  antagonist therapy has been shown by the temporal association of these syndromes with these therapies in 17 patients [25, 26]. Symptoms such as ataxia and dysarthria fluctuated in relation to subsequent treatments and may even culminate, over a period of months, in areflexic flaccid quadriplegia in case of do not stopping immediately the anti-TNF antagonist. GBS developed following infliximab therapy in 10 patients, following etanercept therapy in 5 patients, and following adalimumab therapy in 1 patient. Among the 14 patients for whom follow up data were available, 2 patients experienced no resolution, 9 patients had partial resolution, and 3 patients had complete resolution of GBS following therapy.

### Transverse myelitis

Transverse myelitis (TM) is a segmental spinal cord injury caused by acute inflammation with an approximate incidence of between one to five cases per million population annually [27, 28]. The inflammation of TM is generally restricted to one or two segments, usually in the thoracic cord. Symptoms typically develop rapidly over several hours. Typically the inflammation is bilateral, producing weakness and multimodality sensory disturbance below the level of the lesion. Almost all patients develop leg weakness of varying severity. Arm weakness also occurs if the lesion is in the cervical cord. In addition to diminished sensation, pain and tingling are common and frequently include a tight banding or girdle-like sensation around the trunk, which may be very sensitive to touch. Back and radicular pain are also common. Bowel and bladder dysfunction, reflective of autonomic involvement, also occur. Magnetic resonance imaging (MRI) of the involved section of the spinal cord shows gadolinium-enhancing signal abnormality, usually extending over one or more cord segments. The cord often appears swollen at these levels. Cerebrospinal fluid (CSF) is abnormal in half of patients, with elevated protein level and moderate lymphocytosis. TM is generally a monophasic illness. However, a small percentage of patients may suffer a recurrence [29, 30]. Most patients with idiopathic TM have at least a partial recovery, which usually begins within one to three months. Some degree of persistent disability is common. Patients are often treated with parenteral GC therapy. In most cases of TM anti-TNF-related, the prognosis is favorable with the immediate withdrawal of

the causative drug, together with high-dose courses of GC, intravenous immunoglobulins (IVIG), or plasmapheresis, with partial or complete resolution of the symptoms (occurring spontaneously in some cases) and, sometimes, with persistent imaging abnormalities [31, 32].

### Neuropathy

Peripheral neuropathies can occur early or late after initiation of therapy [1, 4, 7]. Short-term follow-up indicates relatively good outcomes, sometimes after treatment discontinuation alone, although corticosteroids may be necessary to control the condition.

Chronic inflammatory demyelinating polyneuropathy (CIDP, also known as chronic inflammatory demyelinating polyradiculoneuropathy) is an acquired disorder of peripheral nerves and nerve roots. Whether CIDP is a disease or a syndrome remains controversial. CIDP can affect all ages but is more common in older males. It is thought that the disease is more likely to be progressive in the older age group and relapsing-remitting in younger patient .

No specific predisposing factors for CIDP have been identified. There have been conflicting studies on human leukocyte antigen (HLA) type associations, but no clear genetic predisposition has been found. In several case reports, treatment with TNF-antagonist has been associated with the subsequent development of chronic demyelinating neuropathies.

The classic form of CIDP is fairly symmetric and motor involvement is greater than sensory. Weakness is present in both proximal and distal muscles, and this pattern is a hallmark of acquired demyelinating polyneuropath . Cranial nerve and bulbar involvement occur in 10 to 20 percent of patient .

Most patients with CIDP also have sensory involvement and globally diminished or absent reflexes . Sensory impairment in CIDP is usually greater for vibration and position sense than for pain and temperature sense, reflecting the involvement of larger myelinated fibers. Unlike the motor involvement, the sensory involvement tends to follow a distal to proximal gradient, although finger involvement is frequently seen as early as toe and foot involvement. Painful dysesthesias can occur in some patients. Back pain may also be present.

Autonomic involvement in CIDP is generally mild and limited in distribution. Constipation and urinary retention are not usually early symptoms of CIDP, but may occur in more severe cases.

## Conclusions

- Neurologic deficits related to the use of anti-TNF occur in an unpredictable manner and include transverse myelitis, optic neuritis, polycranial neuritis, multiple sclerosis, chronic inflammatory axonal polyradiculoneuropathy, and small fiber polyneuropathy.
- Standardized paraclinical neurological explorations should be proposed to physicians who are in charge of anti-TNF treated patients.
- TNF-alpha blockers are known to potentially cause neurological symptoms which may be part of an MS-like syndrome or represent new inflammatory demyelinating disease. While it is known that TNF-alpha inhibitor drugs can exacerbate multiple sclerosis (MS), there is a question whether this association actually represents an unmasking of pre-existing, pre-symptomatic cases of MS or the development of new demyelinating disease.
- Causal relationship between anti-TNF- $\alpha$  and induction of DD remains unclear, but in some cases the chronology of clinical events is suggestive. Nevertheless, DD might persist despite treatment discontinuation, suggesting that anti-TNF- $\alpha$  could trigger the demyelinating process, which further evolves independently.
- To definitely determine whether a DD is a new onset, anti-TNF alpha related or merely due to latent MS exacerbation we recommend doing MRI of the brain before starting patients on these therapies.
- Current guidelines are to avoid the use of anti-TNF in patients with a history of MS or DD. However, although the overall number of individuals with new onset DD undergoing anti-TNF treatment appears to be small, these episodes can be clinically silent, making it difficult to assess the real number of affected patients.
- The reported rate of demyelination from postmarketing experience likely underestimates the incidence of these events due to underreporting, and the total number of patients exposed being an estimate.
- Prospective postmarketing studies in which the control group includes patients with rheumatic autoimmune diseases-most notably rheumatoid arthritis-treated with conventional therapies could help us to evaluate the real risks and outcomes in patients receiving TNF- $\alpha$  blockers who develop neurological diseases.
- There is a need to establish registries of patients receiving these drugs, including a comparison cohort of patients without these therapies. Possibly we will need to await many years before definite answers are available.

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