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Guillain-Barré and Miller Fisher Syndromes Occurring With Tumor Necrosis Factor α Antagonist Therapy

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Objective. Diverse neurologic syndromes have been described in association with tumor necrosis factor α (TNF α) antagonist therapy for inflammatory arthritides and Crohn's disease. The objective of this study was to review the occurrence and clinical features of Guillain-Barré syndrome and its variant, the Miller Fisher syndrome, during TNF α antagonist therapy.

Methods. The postmarketing database of the US Food and Drug Administration (FDA) was searched, following our experience with a patient with rheumatoid arthritis in whom the Miller Fisher syndrome variant of the Guillain-Barré syndrome developed while he was receiving infliximab therapy.

Results. Our index patient had a neurologic illness defined initially by ataxia and dysarthria, which fluctuated in relation to each subsequent infliximab infusion and, after 6 months, culminated in areflexic flaccid quadriplegia. In addition, 15 patients in whom Guillain-Barré syndrome developed following TNF α antagonist therapy were identified from the FDA database. Guillain-Barré syndrome developed following infliximab therapy in 9 patients, following etanercept therapy in 5 patients, and following adalimumab therapy in 1 patient. Among the 13 patients for whom followup data were available, 1 patient experienced no resolution, 9 patients had partial resolution, and 3 patients had complete resolution of Guillain-Barré syndrome following therapy.

Conclusion. An association of Guillain-Barré syndrome with TNF α antagonist therapy is supported by the worsening of neurologic symptoms that occurred in our index patient following each infusion of infliximab, and by the temporal association of this syndrome with TNF α antagonist therapy in 15 other patients. An acute or subacute demyelinating polyneuropathy should be considered a potential adverse effect of TNF α antagonist therapy.

Tumor necrosis factor α (TNF α) antagonist therapy for inflammatory arthritides and Crohn's disease has been associated with the development of demyelination in the central nervous system and the peripheral nervous system (1,2). The demyelination has been characterized clinically as multiple sclerosis, optic neuritis, transverse myelitis, Guillain-Barré syndrome, or chronic inflammatory demyelinating polyneuropathy (CIDP). One case of Guillain-Barré syndrome occurred during clinical trials of infliximab. Following the marketing of infliximab, 9 cases of Guillain-Barré syndrome or CIDP were reported to the manufacturer (2). Two additional cases of CIDP occurring in association with TNF α antagonist therapy have now been reported (3).

We now report a patient with rheumatoid arthritis in whom ataxia and dysarthria developed while he was receiving infliximab therapy; his neurologic syndrome worsened with successive infusions of infliximab and, after 6 months, culminated as the Miller Fisher syndrome variant of the Guillain-Barré syndrome. In addition, we describe 15 other patients identified from the postmarketing database of the US Food and Drug Administration (FDA) in whom Guillain-Barré syndrome developed while they were receiving TNF α antagonist therapy.

PATIENTS AND METHODS

Database search. The FDA's Adverse Event Reporting System (AERS) database contains postmarketing reports

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of adverse events related to FDA-approved medications. In September 2004, we performed a search of the AERS database for reports of Guillain-Barré syndrome or Miller Fisher syndrome in patients receiving infliximab (Remicade), etanercept (Enbrel), or adalimumab (Humira), using the preferred terms “Guillain-Barré syndrome” and “Miller Fisher syndrome” from the Medical Dictionary for Regulatory Activities. Patients who were included were those in whom Guillain-Barré syndrome or Miller Fisher syndrome was diagnosed in temporal association with TNF α antagonist therapy. A medical literature search in PubMed yielded 1 case report of Guillain-Barré syndrome occurring in association with infliximab therapy (4). This case was in the AERS database and is included in the current report. A second patient with Guillain-Barré syndrome was included in a previous report of demyelination occurring in patients receiving TNF α antagonist therapy (1).

Index patient. A 56-year-old man with seropositive rheumatoid arthritis began therapy with infliximab 21 months prior to hospital admission. He responded well to therapy, which allowed a decrease in the dosage of previously prescribed methotrexate and discontinuation of sulfasalazine. Twenty-four weeks prior to hospital admission, the patient became unsteady while walking. This ataxia developed 6 weeks after his most recent infliximab infusion and 6 days following the administration of influenza vaccine. His ataxia gradually improved, but dysarthria and worsening ataxia developed ~3–4 weeks after each subsequent infusion (Figure 1). The latter symptom progressed transiently to the point at which he was unable to ambulate for 2 weeks.

Fourteen weeks prior to hospital admission, the patient experienced a widespread and persistent eczematous rash with recurrence of ataxia. His ataxia and dysarthria worsened

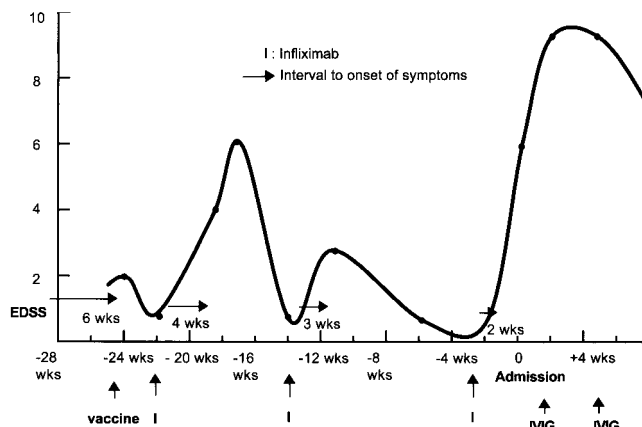


Figure 1. Correlation between clinical course and infliximab infusions in the index patient, showing the temporal relationship between the infliximab infusions and the severity of his neurologic illness. The severity of the patient’s neurologic symptoms was graded using the Expanded Disability Status Scale (EDSS) (16). For this patient, grade 2 corresponded to mild ataxia, grade 4 corresponded to moderate ataxia but ambulating with aid, grade 6 corresponded to dysarthria and inability to ambulate without assistance due to severe ataxia, and grade 9.5 corresponded to quadriplegia with inability to swallow or communicate. IVIG = intravenous immunoglobulin.

again, following an infliximab infusion that was administered 3 weeks prior to hospital admission. Physical examination at the time of hospital admission revealed dysarthric speech, horizontal nystagmus, marked truncal and appendicular dystaxia, and hyperreflexia with withdrawal plantar reflexes. Eczematous skin lesions were present on his lower extremities and torso. The patient’s diagnostic evaluation is shown in Table 1.

One week after he was admitted to the hospital, the patient’s mental status fluctuated, from lethargic to obtunded. By the ninth hospital day, he had a partial right abductor palsy, generalized weakness, and diffuse hyporeflexia. Intravenous methylprednisolone (1,000 mg) was given daily for 2 days, resulting in transient improvement in the patient’s mental status. However, his weakness progressed, leading to paretic dysarthria, poor swallowing, and virtually absent deep tendon reflexes.

Following electrodiagnostic testing, a diagnosis of Miller Fisher syndrome was established. Subsequently, the patient received a 5-day course of intravenous immunoglobulin (IVIG), 0.4 gm/kg/day. His neurologic condition deteriorated further, with development of areflexic flaccid quadriplegia, bifacial and bulbar palsies, and fluctuating mental status. The patient showed rapid improvement after receiving a second course of IVIG therapy. Two months later, he was able to walk with the aid of parallel bars, and at 6 months he was ambulating without use of an assistive device. Seventeen months after hospitalization, double-stranded DNA and RNP autoantibodies were no longer detectable.

RESULTS

We identified 15 patients in the FDA’s postmarketing database in whom Guillain-Barré syndrome developed following TNF α antagonist therapy. Nine of these patients had received infliximab, 5 had received etanercept, and 1 patient had received adalimumab. Supporting clinical and/or diagnostic information was not provided for 2 of these 15 patients. Clinical summaries for the remaining 13 patients and the index patient are provided in Table 2. The median age of these 14 patients was 56 years (range 34–81 years). The median interval from the first administration of TNF α antagonist therapy to the onset of Guillain-Barré syndrome was 4 months (range 1.5 months to 2 years; $n = 11$ patients). Electrodiagnostic findings that supported the diagnosis of Guillain-Barré syndrome were reported in 9 patients. In 6 patients, antecedent events included upper respiratory tract infection, flu-like illness, or low-grade fever, and in 1 patient the antecedent event was a fever of unknown origin. Thirteen patients received therapy for Guillain-Barré syndrome, which included plasmapheresis, IVIG, and/or corticosteroids.

Nine patients experienced partial resolution, and 3 patients had complete resolution of Guillain-Barré syndrome. One patient continued to have symptoms,

Table 1. Laboratory findings in the index patient*

Test	Result
Cerebrospinal fluid analyses	1st hospital day: 121 NBC (95% lymphocytes), protein 67 mg/dl, glucose 54 mg/dl, IgG 10.7 mg/dl. 19th hospital day: 36 NBC, protein 79 mg/dl. 35th hospital day: 0 NBC, protein 57 mg/dl. Negative for herpes simplex virus, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, enterovirus, and arboviruses, by polymerase chain reaction.
Serologic tests	GQ1b IgG antibody titer <1:100; HIV negative; Lyme antibody negative; rheumatoid factor 68 IU/ml; ANA titer 1:640, homogeneous (ANA negative at diagnosis 2 years earlier); dsDNA antibody titer 1:20 (<i>Crithidia luciliae</i> assay); RNP antibody positive.
Electromyography/nerve conduction	12th day: absent F-wave responses from both median and the right ulnar nerves and prolongation of the F wave response from the left peroneal nerve (indicative of a proximal conduction block). 28th day: absence of F waves in 6 motor nerves and no electrical response from the peroneal, superficial peroneal, sural, and left ulnar nerves.
Magnetic resonance imaging	Brain: age-related microvascular white matter changes (31 days prior to hospital admission and on 3rd, 10th, and 21st hospital days). Cervical, thoracic, and lumbar spines: normal.
Cerebral angiography	Normal.
Electroencephalography	Normal.
Skin biopsy	Subacute spongiotic dermatitis with intraepithelial microabscesses and dermal perivascular mononuclear cell infiltrate with scattered neutrophils and eosinophils.

* NBC = nucleated blood cell; HIV = human immunodeficiency virus; ANA = antinuclear antibody; dsDNA = double-stranded DNA.

and the outcome of the remaining 3 patients is unknown. Two patients who experienced partial resolution had a relapsing course, in which the neurologic symptoms improved and then recurred without further exposure to a TNF α antagonist. In the index patient, ataxia improved but recurred along with worsening neurologic symptoms upon further exposure to infliximab (positive rechallenge). Another patient had a positive rechallenge, in which her acute neuromuscular weakness recurred following a subsequent infliximab infusion. However, 2 patients experienced no recurrence of Guillain-Barré syndrome when TNF α antagonist therapy was reinitiated several months after the event (negative rechallenge); in 1 of these patients the rechallenge involved a lower dose of infliximab.

DISCUSSION

We report 16 patients in whom Guillain-Barré syndrome developed in association with TNF α antagonist therapy. These cases of Guillain-Barré syndrome may have occurred as a consequence of this biologic

therapy or as a consequence of an unrelated triggering event, such as an antecedent infection. However, positive temporal relationships with TNF α antagonist therapy in all of the patients support the first possibility. Six patients had a preceding upper respiratory tract infection, flu-like illness, or low-grade fever, and the index patient had received influenza vaccine 6 days before the onset of ataxia. Nevertheless, the role of TNF α antagonist therapy could not be excluded, despite the presence of antecedent events that possibly triggered Guillain-Barré syndrome in several patients.

Guillain-Barré syndrome is the most frequent cause of acute or subacute flaccid paralysis. The clinical course of this inflammatory polyradiculoneuropathy is typically monophasic. Guillain-Barré syndrome comprises a heterogeneous group of conditions defined by varying clinical, electrophysiologic, and pathologic features (5). One variant is the Miller Fisher syndrome, which comprises ~3–5% of Guillain-Barré syndrome cases in Western countries and is characterized by the triad of ataxia, external ophthalmoplegia, and areflexia.

Table 2. Characteristics of Guillain-Barré syndrome occurring with TNF α antagonist therapy*

Age/sex	Indication	Drug/duration of therapy/no. of infusions	Clinical signs and symptoms	Antecedent events	EMG/NC	Therapy	Outcome
56/M†	RA	Infliximab/15 months/12	Ataxia, dysarthria progressing to areflexic quadriplegia	Flu vaccine	Demyelinating polyneuropathy with proximal conduction defect	IVIG, methylprednisolone	Partial resolution at 3.5 months; positive rechallenge with subsequent 3 infusions
49/F	Crohn's disease	Infliximab/several years/2	Weakness, respiratory distress	Low-grade fever of short duration	Acute demyelinating polyneuropathy	IVIG	Not reported
66/F	RA	Infliximab/8 months/6	Progressive weakness and imbalance		Not reported	IVIG	No response to therapy
56/F	RA	Infliximab/6 months/4	Symmetric quadriparesis	URI	Axonal polyneuropathy	IVIG	Partial resolution at 2 weeks
43/M	Psoriatic arthritis	Infliximab/5 months/5	Ascending progressive quadriparesis, urinary retention		Acute demyelinating polyneuropathy	Not reported	Partial resolution at 2 weeks
62/M	RA	Infliximab/3–4 months/4	Progressive ascending paralysis, paresthesia of legs, inability to walk	Fever of unknown origin	Not reported	IVIG, plasmapheresis, mechanical ventilation	Partial resolution at 10 months
34/M‡	Psoriatic arthritis	Infliximab/3.5 months/2	Ascending paralysis	URI; MFS 14 years earlier	Demyelinating polyradicular neuropathy	Mechanical ventilation, IVIG	Complete resolution at 3 weeks; negative rechallenge at 1 month
81/F	RA	Infliximab/not reported/4	Weakness, paresthesia, decreased diaphragmatic function		Normal at 1 week	IVIG, plasmapheresis	Relapse off-drug; partial resolution
41/F	Crohn's disease	Infliximab/not reported/2	Acute neuromuscular weakness; preexisting myotonic dystrophy		Demyelinating polyneuropathy	Not reported	Partial resolution; positive rechallenge after each infusion
58/F	RA	Etanercept/2 years	Progressive ascending paralysis, paresthesia of arms and face	Flu-like illness	Not reported	IVIG, steroid	Multiple relapses over 6 months off-drug; partial resolution at >9 months
58/F	RA	Etanercept/4 months	Progressive weakness and difficulty ambulating		Demyelinating polyneuropathy	IVIG	Complete resolution at 6 weeks
53/M§	RA	Etanercept/2.5 months	Progressive quadriparesis, paresthesia		Polyradicular neuropathy	Plasmapheresis	Partial resolution at 1 week
36/F	RA	Etanercept/not reported	Paresthesia of upper and lower extremities	URI	Not reported	IVIG	Complete resolution; negative rechallenge at 3 months
61/F	RA	Adalimumab/1.5 months	Progressive quadriparesis, hyporeflexia, hypoesthesia in foot	Flu-like illness	Axonal motor-sensory polyneuropathy	IVIG	Partial resolution at 1 month

* TNF α = tumor necrosis factor α ; EMG/NC = electromyogram/nerve conduction; RA = rheumatoid arthritis; IVIG = intravenous immunoglobulin; URI = upper respiratory tract infection; MFS = Miller Fisher syndrome.

† Index case.

‡ Literature case (4).

§ Literature case (1).

Antibodies to ganglioside GQ1b are detected in 80–90% of patients.

The index patient presented with cerebellar ataxia and nystagmus and ultimately experienced an areflexic flaccid quadriplegia and bifacial and bulbar palsies. This sequence of clinical events is consistent with progression of the Miller Fisher syndrome to a generalized form of Guillain-Barré syndrome. Several features of the index patient's Guillain-Barré syndrome point to induction of the syndrome by infliximab; these features include the temporal association of disease development with infliximab therapy, the unusually protracted prodrome, and the coincidental development of a skin rash (which was considered to be drug-related) and lupus-related autoantibodies. Finally, the index patient improved dramatically over 2 months after discontinuation of infliximab and treatment with IVIG. The prognosis of Guillain-Barré syndrome is highly dependent on the level of disease severity, and recovery may continue for up to 2 years in patients who are affected as severely as was the index patient (6).

It would be desirable to assess outcomes and resolution rates in each of the patients in this series. Unfortunately, only limited information is available in some of the reports. The outcome of 3 patients and complete information about the severity of the Guillain-Barré syndrome in many of the reported patients were not provided. Accordingly, we cannot compare the resolution rates among the postmarketing cases with those in other Guillain-Barré syndrome cohorts.

Guillain-Barré syndrome was temporally associated with infliximab therapy in 10 patients and with etanercept therapy in 5 patients; except for 1 case involving infliximab, all of the cases occurred in the US. The only case reported in association with adalimumab came from outside the US. In the US, ~303,000 patients have received infliximab from the time of its approval in August 1998 to August 2004 (Centocor: unpublished data). An estimated total of 280,000 patients in the US received etanercept from the time of its approval in November 1998 to January 2005 (Amgen: unpublished data). This compares with an annual incidence of Guillain-Barré syndrome of 1–3/100,000 population (7). However, these data should be interpreted cautiously, because significant underreporting is known to occur in a postmarketing surveillance system. An examination of large epidemiologic databases will be necessary to determine the true incidence of drug-related adverse events.

Guillain-Barré syndrome is thought to arise from

an aberrant immune response to peripheral nerve myelin or axons, triggered by an antecedent event such as infection. Such infections are reported by two-thirds of patients with Guillain-Barré syndrome, and the etiologic agents include *Campylobacter jejuni*, cytomegalovirus, Epstein-Barr virus, varicella-zoster virus, *Hemophilus influenzae*, and *Mycoplasma pneumoniae* (7). In epidemiologic studies, the risk of developing Guillain-Barré syndrome following influenza vaccination is reported to be slightly increased (8). In such cases, epitopes shared between the infectious organism and nerve fibers are thought to be targets for an aberrant cross-reactive immune response (molecular mimicry) (9). Susceptibility to the development of Guillain-Barré syndrome is likely dependent on subsequent events, influenced in part by the immunogenetic background of the host.

Synergy between cellular and humoral immune responses to unknown peripheral nerve antigens has been postulated to underlie the immunopathogenesis of Guillain-Barré syndrome. High levels of markers of T cell activation have been demonstrated in the serum of patients with Guillain-Barré syndrome (10). TNF α and other cytokines have been implicated in the pathogenesis of Guillain-Barré syndrome. Levels of TNF α are elevated in the serum of affected patients, correlate (in many studies) with disease severity, and normalize in parallel with the clinical recovery of patients (11). These observations support a proinflammatory function of TNF α in Guillain-Barré syndrome.

TNF α has also been shown to have immunoregulatory functions. It suppresses T cell reactivity to autoantigens in animal models of autoimmunity (12). TNF α deficiency leads to failed regression of myelin-specific T cell reactivity and prolonged survival of activated T cells (13). When endogenous TNF α is blocked by repeated injections of a TNF α antagonist, T cell proliferative responses and cytokine production are enhanced (12). The prolonged administration of TNF α antagonists is thought to enhance autoimmune responses by potentiating T cell receptor signaling and decreasing apoptosis of autoreactive T cells (14). A systemically administered TNF α antagonist potentially could enter the peripheral nervous system at the roots and motor nerve terminals, where the blood–nerve barrier is absent or relatively deficient. If this occurs, TNF α within the peripheral nervous system compartment is neutralized or reduced. Too little TNF α may augment or prolong the myelin-specific T cell response and increase the risk of developing or prolonging an immune-mediated neuropathy (15).

TNF α antagonist therapy could promote the development of Guillain-Barré syndrome by augmenting

the number of activated peripheral T cells or by disturbing the intrinsic balance of TNF α and its receptors in the local peripheral nervous system compartment. These factors, alone or in combination, could induce the clinical expression of Guillain-Barré syndrome in immunogenetically susceptible patients. Guillain-Barré syndrome is typically a self-limited, monophasic disease. Our index patient had been receiving TNF α antagonist therapy for 15 months before the initial development of neurologic symptoms. Each episode of these symptoms was similar but recurred, on average, 3.5 weeks following the subsequent 3 infusions of infliximab. His neurologic symptoms increased with cumulative exposure to the biologic agent, and the flares that occurred after each infliximab infusion were longer and more severe. A prolonged and intensified pathogenic autoimmune response, induced by TNF α antagonist therapy, could explain the patient's symptom flares that occurred following each infliximab infusion. Two of the other patients reported here had unusual relapsing courses. We postulate that the duration and the extent of exposure to a TNF α antagonist may permit development of an atypical autoimmune response once the disease is induced.

The safety of TNF α antagonist therapy is a crucial issue, because use of such therapy is increasing every year, particularly following its approval for additional indications. In this report, we summarized a series of patients in whom Guillain-Barré syndrome developed in association with TNF α antagonist therapy. Although a causal relationship between Guillain-Barré syndrome and TNF α antagonist therapy cannot be proven, clinicians should monitor patients who are receiving TNF α antagonist therapy for neurologic signs and symptoms suggestive of demyelinating disease in either the central or peripheral nervous system.

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