Long-term Course of Demyelinating Neuropathies Occurring During Tumor Necrosis Factor-α–Blocker Therapy

Pierre Lozeron, MD; Christian Denier, MD, PhD; Catherine Lacroix, MD; David Adams, MD, PhD

Objective: To report the long-term follow-up (mean, 41 months; range, 25-55 months) of patients with demyelinating neuropathy occurring after tumor necrosis factor-α (TNF-α) blocker treatment (infliximab [Remicade], etanercept [Enbrel], and adalimumab [Humira]).

Background: Demyelinating neuropathy is a rare adverse event of anti–TNF-α therapy. Improvement usually occurs after drug interruption and/or in association with usual treatments for demyelinating neuropathies.

Design: Case report with review of the previously published cases.


Patients: Five patients (4 men, mean age, 47 years) who developed a demyelinating neuropathy during anti–TNF-α therapy.

Main Outcome Measure: Development of neuropathy.

Results: Neuropathy developed early (8 months) after treatment introduction. Various clinical patterns were encountered, including pure sensory neuropathy. Immuno-modulating treatments were always required for neuropathy control. Chronic demyelinating neuropathy developed either after change of anti–TNF-α drug or spontaneously after treatment discontinuation without any drug reintroduction.

Conclusion: Influence of anti–TNF-α treatment continuation on the long-term course of neuropathy is variable, suggesting that anti–TNF-α treatment withdrawal is not always necessary for neuropathy control.

Arch Neurol. 2009;66(4):490-497

METHODS

Five patients (4 men, mean age, 47 years) were referred for a peripheral nerve disorder during anti–TNF-α therapy. Patient histories and clinical course are detailed later and summarized in Figure 1 and Table 2. Nerve con-
demyelinating neuropathy was confirmed by nerve biopsy. Other detectable causes of neuropathy, including monoclonal gammopathy, were excluded at initial workup.

Abbreviations: AS, ankylosing spondylitis; CB, conduction block; GBS, Guillain-Barré syndrome; IVIG, intravenous immunoglobulin; IV MP, intravenous methylprednisolone; MMN, multifocal motor neuropathy; ND, not determined; PE, plasma exchange; PN, polyneuropathy; RA, rheumatoid arthritis; S, sensory; SM, sensory motor; TNF, tumor necrosis factor.

**Case 1**

A 39-year-old man was referred for acute multifocal neuropathy. He presented with a 15-year history of hidradenitis suppurativa. Several antibiotic regimens were given without improvement. Infliximab (Remicade) (5 mg/kg per infusion) administration was then started. Five injections were administered without obvious clinical improvement (0, 2, 6, 12, and 18 weeks). A few hours after the fifth injection (total cumulative dose, 2175 mg), the patient noticed weakness and tingling sensations in the right hand and toes, which led to immediate treatment discontinuation. Symptoms did not progress during the following weeks.

On neurological examination, the patient presented with a right hand weakness in ulnar and median distal innervated muscles (Medical Research Council score, 3/5) and in the right biceps and brachioradialis muscles (4/5). Tendon reflexes were weak in the right arm. Slight diffuse reduced pinprick sensation was noticed in the right hand. Nerve conduction studies showed motor neuropathy with conduction blocks (Table 3). The patient initially declined IVIG infusions. Five months after onset, while the neurological status remained unchanged, he asked to be treated. The month following a 1 g/kg–IVIG

### Table 1. Clinical and Paraclinical Patterns of Published Cases of Demyelinating Neuropathies Occurring After Anti–TNF–α Treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Underlying disease</th>
<th>Anti–TNF–α drug</th>
<th>Cumulative dose</th>
<th>Duration of treatment at onset</th>
<th>Type of neuropathy</th>
<th>Course of neuropathy</th>
<th>Nerve biopsy</th>
<th>Neurorapy treatment</th>
<th>Duration of follow-up</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Psoriasis arthritis</td>
<td>Infliximab</td>
<td>300 mg 6 mo</td>
<td>3-13 mo</td>
<td>GBS</td>
<td>Acute</td>
<td>None</td>
<td>IVIG</td>
<td>2 y</td>
<td>Complete</td>
</tr>
<tr>
<td>2</td>
<td>Crohn disease in 1; collagenous colitis and seronegative arthritis in 1</td>
<td>Infliximab</td>
<td>540-1000 mg ND 3 mo-2 y</td>
<td>Acute in 2; chronic in 1</td>
<td>MMN</td>
<td>Chronic</td>
<td>None</td>
<td>None</td>
<td>3-5 wk</td>
<td>Partial to marked</td>
</tr>
<tr>
<td>3</td>
<td>RA</td>
<td>Infliximab</td>
<td>720 mg 14 wk</td>
<td>ND</td>
<td>Lewis-Sumner syndrome</td>
<td>Acute or ND</td>
<td>None</td>
<td>None</td>
<td>13 mo</td>
<td>Marked</td>
</tr>
<tr>
<td>4</td>
<td>RA in 1; AS in 1</td>
<td>Infliximab</td>
<td>1.5 mo to several years; ND in 2</td>
<td>Acute in 2; chronic in 1</td>
<td>MMN; axonal S PN</td>
<td>Acute</td>
<td>None</td>
<td>None</td>
<td>6-8 mo</td>
<td>Partial to marked</td>
</tr>
<tr>
<td>5</td>
<td>RA in 11; Crohn disease in 2; psoriatic arthritis in 2</td>
<td>Infliximab</td>
<td>720-4000 mg ND 5-13 mo</td>
<td>Chronic</td>
<td>Lewis-Sumner syndrome in 1; MMN in 1; S or SM PN in 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Duration of Follow-up

- Infliximab (Remicade) (5 mg/kg per infusion) administration was then started.
- Five injections were administered without obvious clinical improvement.
- Five months after onset, while the neurological status remained unchanged, he asked to be treated.
- The month following a 1 g/kg–IVIG

**REPORT OF CASES**

**Case 1**

A 39-year-old man was referred for acute multifocal neuropathy. He presented with a 15-year history of hidradenitis suppurativa. Several antibiotic regimens were given without improvement. Infliximab (Remicade) (5 mg/kg per infusion) administration was then started. Five injections were administered without obvious clinical improvement (0, 2, 6, 12, and 18 weeks). A few hours after the fifth injection (total cumulative dose, 2175 mg), the patient noticed weakness and tingling sensations in the right hand and toes, which led to immediate treatment discontinuation. Symptoms did not progress during the following weeks.

On neurological examination, the patient presented with a right hand weakness in ulnar and median distal innervated muscles (Medical Research Council score, 3/5) and in the right biceps and brachioradialis muscles (4/5). Tendon reflexes were weak in the right arm. Slight diffuse reduced pinprick sensation was noticed in the right hand. Nerve conduction studies showed motor neuropathy with conduction blocks (Table 3). The patient initially declined IVIG infusions. Five months after onset, while the neurological status remained unchanged, he asked to be treated. The month following a 1 g/kg–IVIG

**REPORT OF CASES**

**Case 1**

A 39-year-old man was referred for acute multifocal neuropathy. He presented with a 15-year history of hidradenitis suppurativa. Several antibiotic regimens were given without improvement. Infliximab (Remicade) (5 mg/kg per infusion) administration was then started. Five injections were administered without obvious clinical improvement (0, 2, 6, 12, and 18 weeks). A few hours after the fifth injection (total cumulative dose, 2175 mg), the patient noticed weakness and tingling sensations in the right hand and toes, which led to immediate treatment discontinuation. Symptoms did not progress during the following weeks.

On neurological examination, the patient presented with a right hand weakness in ulnar and median distal innervated muscles (Medical Research Council score, 3/5) and in the right biceps and brachioradialis muscles (4/5). Tendon reflexes were weak in the right arm. Slight diffuse reduced pinprick sensation was noticed in the right hand. Nerve conduction studies showed motor neuropathy with conduction blocks (Table 3). The patient initially declined IVIG infusions. Five months after onset, while the neurological status remained unchanged, he asked to be treated. The month following a 1 g/kg–IVIG

**REPORT OF CASES**

**Case 1**

A 39-year-old man was referred for acute multifocal neuropathy. He presented with a 15-year history of hidradenitis suppurativa. Several antibiotic regimens were given without improvement. Infliximab (Remicade) (5 mg/kg per infusion) administration was then started. Five injections were administered without obvious clinical improvement (0, 2, 6, 12, and 18 weeks). A few hours after the fifth injection (total cumulative dose, 2175 mg), the patient noticed weakness and tingling sensations in the right hand and toes, which led to immediate treatment discontinuation. Symptoms did not progress during the following weeks.

On neurological examination, the patient presented with a right hand weakness in ulnar and median distal innervated muscles (Medical Research Council score, 3/5) and in the right biceps and brachioradialis muscles (4/5). Tendon reflexes were weak in the right arm. Slight diffuse reduced pinprick sensation was noticed in the right hand. Nerve conduction studies showed motor neuropathy with conduction blocks (Table 3). The patient initially declined IVIG infusions. Five months after onset, while the neurological status remained unchanged, he asked to be treated. The month following a 1 g/kg–IVIG
Figure 1. Clinical course of patients with demyelinating neuropathy during anti–tumor necrosis factor-α (TNF-α) treatment. IVIG indicates intravenous immunoglobulin; PE, plasma exchange; RA, rheumatoid arthritis; AS, ankylosing spondylitis; time, time in months to symptom onset.
infusion, he experienced a dramatic improvement, with only slight residual weakness in the right hand. Twenty-six months after onset, he remained mildly affected.

**CASE 2**

A 45-year-old, right-handed man was referred for a subacute multifocal neuropathy. He has presented with a 15-year history of psoriasis. For 9 years, the patient had been treated for psoriatic arthritis with nonsteroidal anti-inflammatory drugs and methotrexate. Because of refractory arthritis, infliximab treatment was begun (5 mg/kg per infusion at weeks 0, 4, and 6). After initial improvement, the clinical condition deteriorated and the patient received etanercept (30 mg/wk for 6 months). Because of progressive loss of efficacy, etanercept was substituted with infliximab (5 mg/kg). During the last infusion (total cumulative dose, infliximab, 2250 mg; etanercept, 1200 mg), the patient presented with hyperthermia considered as a general adverse effect of the treatment. During the following 8 weeks, he progressively noticed right hand weakness with amyotrophy in the first dorsal interosseus muscle. On clinical examination, he presented with a clawhand and slight amyotrophy in the ulnar nerve territory. Muscle strength was reduced in the right interossei muscles (4/5), flexor carpi radialis (4/5), and flexor digitorum sublimis and communis and extensor carpi radialis (3+/5). Tendon reflexes and sensory examination results were normal. Nerve conduction study showed multifocal motor neuropathy with conduction blocks in the arms (Table 3). The cerebrospinal fluid protein level was slightly elevated (0.6 g/L). Anti–TNF-α treatment was stopped and the patient was treated with monthly IVIG infusions (twice, 2 g/kg) without efficacy. Subsequently, plasma exchanges were started on alternate days for 4 exchanges and then every month for 11 months. Because of the lack of treatment efficacy, the 3 following monthly exchanges were associated with 2 g/kg–IVIG infusions. In 3 months, the patient fully recovered.

**CASE 3**

A 40-year-old man was referred for asymmetric sensorimotor neuropathy. He had been treated with TNF-α blockers for 5 years for ankylosing spondylitis and psoriasis. The first months, the patient was treated with etanercept (50 mg/wk). When he started to complain of paresthesiae in the last right 3 fingers and in both feet,
the treatment was stopped and the patient recovered. Every second week, 40-mg adalimumab (Humira) infusions were then initiated but interrupted after 11 months because of lack of efficacy. Infliximab was then prescribed (6 infusions of 5 mg/kg administered every 8 weeks, followed by 3 infusions of 5 mg/kg every 6 weeks). Six weeks after treatment, the dose was doubled to 10 mg/kg (total cumulative dose, 4200 mg) and symptoms reappeared. The patient developed right foot drop and paresthesiae in all 4 limbs. Infliximab treatment was stopped. On clinical examination, he presented with weakness in tibialis anterior (3/5 on the right side and 4/5 on the left side) and in both interossei (4/5). Tendon reflexes were absent. Position sense was abnormal in the feet. Pinprick sensation was reduced bilaterally in the legs and in the fingers. Nerve conduction studies were suggestive of demyelination with some prolonged distal motor latencies and F waves and conduction block on the right peroneal nerve (Table 3). Lumbar magnetic resonance imaging results and cerebrospinal fluid protein level were normal. Right superficial radial nerve biopsy revealed slightly reduced myelinated fiber density, demyelinated fibers, and thinly remyelinated fibers (Figure 2A). Teased fiber preparation showed demyelination.
eliminated-remyelinated fibers (Figure 2B). After 2 monthly IVIG infusions (1 g/kg and then 2 g/kg), the patient experienced a dramatic improvement with slight residual weakness of the right tibialis anterior muscle. The patient remained clinically stable for 5 months but the neuropathy relapsed without any reintroduction of anti–TNF-α therapy. It required IVIG infusion, leading to complete remission.

CASE 4

A 60-year-old woman was referred for numbness in the toes. She presented with a 30-year history of Crohn disease and tuberculous spondylitis. She had previously been given phenylbutazone and sulfasalazine for a 34-year history of ankylosing spondylitis with various efficacy. Then, 7 infusions of infliximab were administered (5 mg/kg per infusion). After 6 months (total cumulative dose, 3360 mg), the patient complained of numbness in the feet, unsteadiness of gait with falls, weakness in the legs, and tingling sensations in the hands. On neurological examination, strength was reduced in the anterior tibialis and extensor digitorum brevis muscles (3/5). Tendon reflexes were absent in all 4 limbs. Vibratory sensation was reduced in the feet and both pinprick and thermal sensations were reduced up to the knees. The spinal protein level was slightly elevated (0.7 g/L). Nerve conduction studies showed a moderate mixed sensory motor neuropathy (Table 3). A left peroneal sensory nerve biopsy specimen showed slightly reduced myelinated nerve fiber density. Teased fiber preparation revealed remyelinating fibers after segmental demyelination and tomacula. Because of the neuropathy, infliximab (Remicade) administration was stopped. Etanercept treatment was initiated (50 mg per week) and simultaneously the patient was treated with IVIG (1 g/kg, then 2 g/kg after 1 month) with no effect. Subsequently, using 20-mg prednisone per day, her condition improved dramatically for 1 year. Two years after onset, while the steroid treatment had been progressively stopped, the patient’s symptoms returned. Prednisone was reintroduced (20 mg/d) with virtually no effect after 6 months. Coadministration of azathioprine led to partial improvement of her symptoms after failure of a new IVIG infusion. Four years after onset, the patient was still treated with Enbrel (25 mg twice a week) and the neuropathy was still disabling (unsteadiness of gait and paresthesiae of all 4 extremities).

CASE 5

This 50-year-old patient was referred for progressive sensory polyneuropathy. He presented with a 6-year history of rheumatoid arthritis. He had been successively treated with hydroxychloroquine, methotrexate, and sulfasalazine without improvement. Every second week, 40-mg adalimumab (Humira) infusions were initiated. Concomitantly, he began to complain of tingling sensations in both hands and of burning feet. Temporarily, the rheumatological disease improved, but progressively, the patient lost benefit of treatment. Two years after onset of anti–TNF-α treatment, the adalimumab dosage was increased by 40 mg every week (total cumulative dose, >4000 mg) in association with prednisone (15 mg/d). Then, the patient experienced worsening of his sensory symptoms in all 4 limbs. On clinical examination, strength and all deep tendon reflexes were normal. He did not have pes cavus. Pinprick and temperature sensations were reduced in a stocking-glove distribution. Vibratory sensation was reduced in both hands. Position sense and Romberg test results were normal. Nerve conduction studies were diagnostic of demyelinating polyneuropathy according to American Academy of Neurology criteria15 (Table 3). The spinal protein level was elevated (0.8 g/L). The right sural nerve biopsy showed normal myelinated fiber density, few fibers with reduced myelin thickness, and onion bulbs. Teased fiber preparations revealed remyelinating fibers after segmental demyelination. Considering the slight neurological disability, as well as for rheumatological reasons, anti–TNF-α treatment was not discontinued but a 50% dosage reduction was decided. After 2 years, he was still treated with weekly infusions of 20-mg adalimumab plus prednisone (5 mg/d) and remained stable in good neurological condition with slight numbness in the toes.

Demyelinating neuropathies are rare adverse events of anti–TNF-α therapy. Previous series emphasized the development of acute or chronic demyelinating neuropathy usually occurring a few months after the onset of TNF-α treatment, very often associated with conduction blocks on nerve conduction studies. The prognosis is usually good, without relapse, sometimes only after usual treatments for demyelinating neuropathies.4,5,7-10,12 (Figure 1).

Our series disclosed a new clinically pure sensory pattern associated with severely reduced sensory nerve conduction and pathological changes in sural nerve biopsy...
typical of demyelination. In the remainder, patients presented with more classic motor or sensory motor neuropathy with demyelinating features on nerve conduction studies, including conduction blocks or severely reduced motor or sensory conduction velocity (Table 3). To confirm demyelination, a nerve biopsy was performed in 3 patients because conduction blocks can erroneously point toward demyelination in rare cases of vasculitis. Moderate axonal loss, demyelinating and remyelinating fibers on semithin sections, absence of cell infiltration or vascular lesions on paraffin sections, and demyelinating features on teased fiber preparation were the hallmark of these specimens. They confirmed the demyelinating origin of the neuropathy. In the 2 remaining patients, stringent electrophysiological criteria for conduction block persistent on consecutive nerve conduction studies were considered diagnostic for demyelination excluding the possibility of mononeuropathy multiplex. According to Rankin score, mild (patient 5) to severe (patients 1 and 2) incapacity was noticed, usually occurring during the first months of treatment (range, 3-13 months; mean, 8 months) (Figure 1). Anti–TNF-α treatment withdrawal was tested in 3 patients without efficiency on clinical symptoms (patients 1, 2, and 3), which indicates that spontaneous outcome after treatment discontinuation is sometimes worse than previously described. Because of neurological disability, most patients required usual treatments for demyelinating neuropathies, which led to various outcomes. Patients 1 and 3 markedly improved with IVIG therapy and patient 2, only with the association of IVIG therapy and plasma exchange. In 2 patients (patients 4 and 5) with mild neuropathy, anti–TNF-α treatment was not withdrawn, at their referring physician's request, because of the good clinical response of their underlying pathology. Both still have persistent symptoms, disabling in 1 (patient 4), indicating that outcome of treated patients is sometimes poor.

Our long-term follow-up indicates that a chronic demyelinating neuropathy can develop in some patients. After a spontaneous complete remission following treatment interruption, patient 3 presented with the first reported relapse in the absence of any anti–TNF-α treatment reintroduction. In patient 4, neuropathy remained poorly controlled in spite of coadministration of steroids and azathioprine. At last examination (mean follow-up duration, 3 years; range, 25-55 months), 4 of our 5 patients had mild to moderate disability.

Our series offers new insights in the pathophysiology of demyelinating neuropathies occurring during TNF-α inhibitor therapy. The primary immune conditions of patients 4 and 5 (Crohn disease and rheumatoid arthritis) should probably be considered as a contributing factor to the neuropathy. Furthermore, patient 5, with clinically pure sensory demyelinating neuropathy, could be considered as having sensory chronic inflammatory demyelinating polyradiculoneuropathy but without indication on its etiology. The close temporal association between neuropathy onset and anti–TNF-α dosage increase suggests a drug-related mechanism instead of idiopathic sensory chronic inflammatory demyelinating polyradiculoneuropathy. Although some authors do not consider demyelinating neuropathies as autoimmune diseases induced by anti-TNF agents, patient 1 was not affected by an underlying dysimmune disease, strengthening the drug-induced dysimmunity hypothesis. Furthermore, the absence of cellular infiltration in the nerve biopsy specimen of our 3 patients is in accordance with a primarily humoral mechanism suggested by others. The decision to definitively stop anti–TNF-α therapy should be discussed case by case between the rheumatologist and the neurologist. Our data tend to show that once anti–TNF-α blockers have triggered a demyelinating neuropathy, the ensuing course of the neuropathy is unpredictable, with or without drug interruption. Spontaneous relapse can occur (patient 3) without anti-TNF treatment reintroduction, and on the contrary, 1 of the 2 patients who pursued anti–TNF-α treatment stabilized with minimal residual symptoms after drug dosage reduction. This is of critical importance in many patients who benefit from anti–TNF-α treatment for their underlying disease. Drug interruption should probably be limited to patients with ongoing disabling neuropathies and controlled underlying affections. Furthermore, efficacy of usual treatments for demyelinating neuropathies indicates that the management and monitoring of these patients should be similar to that for idiopathic demyelinating neuropathies and should be undertaken under the supervision of a neurologist.

Accepted for Publication: October 7, 2008.
Correspondence: Pierre Lozeron, MD, Service de Neurologie, Centre Hospitalier de Bicêtre, 94275 Le Kremlin Bicêtre, France (pierre.lozeron@bct.aphp.fr).

Author Contributions: Study concept and design: Lozeron and Adams. Acquisition of data: Lozeron, Denier, and Lacroix. Analysis and interpretation of data: Lozeron, Denier, and Adams. Drafting of the manuscript: Lozeron and Lacroix. Critical revision of the manuscript for important intellectual content: Denier and Adams. Administrative, technical, and material support: Lacroix. Study supervision: Adams.

Financial Disclosure: None reported.

Additional Contributions: T. Bardin, MD, A. Blancher, MD, M. G. Bousser, MD, M. Breban, MD, PhD, P. Corlobe, MD, Agnes Levy, MD, Annabelle Levy, MD, and P. Seror, MD, referred patients and performed some of the nerve conduction studies. Michael Dubow, MD, provided editing assistance.

REFERENCES


**Correction**

In the Original Contribution entitled “Epidemic Ataxia Associated With EAAT1 Mutation C186S Affecting Glutamate Reuptake,” by de Vries et al, published in the January issue of the Archives (2009;66[1]:97-101), incorrect y-axis length and labeling appears in Figure 2C. The y-axis now extends to a value of 120 and should read as follows: “Glutamate Uptake (pmol/mg protein/min).” The corrected Figure 2C appears here.

**Figure 2.** EAAT1 C1865 mutation. A, Schematic representation of the EAAT1 protein and the location of the mutated Cys186 amino acid in transmembrane segment 4B (indicated by a black dot) (the structure is adapted from Yernool et al14). B, Conservation of the mutated residue Cys186 highlighted in gray. The protein sequences were obtained from GenBank (homo sapiens, NP_004163; Bos taurus, NM_001083750; Mus musculus, NP_683740; Rattus norvegicus, NP_062098; salmonader, O57321; Danio rerio, NP_477428; Drosophila melanogaster, NP_497985; human EAAT2, NP_006662; human EAAT3, NP_044161; human EAAT4, NP_005062; human EAAT5, NP_006662). C, Glutamate uptake assay in COS7 cells expressing mutant EAAT1-186S (mean [SEM], 88.2[5.5]) or wild-type EAAT1-186C (mean [SEM], 107.8[6.9]). The results are the mean (SEM) of the 4 experiments, each in triplicate. The values are picomoles of glutamate transported per milligram of protein per minute of incubation. Asterisk indicates significant reduction of glutamate uptake compared with wild type (P=.029). Error bars indicate SEM. HP indicates helical hairpin.

©2009 American Medical Association. All rights reserved.

*Reprinted with Corrections*