Tumor Necrosis Factor - Alpha and Neuropathy

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CME Information
Product: JR18 - Tumor Necrosis Factor - Alpha and Neuropathy

Course Description
Tumor necrosis factor (TNF-) plays an important role in many aspects of immune system development, immune-response regulation, and T-cell-mediated tissue injury. The evidence that TNF-, released by autoreactive T cells and macrophages, may contribute to the pathogenesis of immune-mediated demyelinating neuropathies is reviewed. TNF- antagonists (infliximab, etanercept, adalimumab) are indicated for the treatment of advanced inflammatory rheumatic and bowel disease, but these drugs can induce a range of autoimmune diseases that also attack the central and peripheral nervous systems. Case histories and series report on the association between anti-TNF- treatment and various disorders of peripheral nerve such as Guillain-Barré syndrome, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex, and axonal sensorimotor polyneuropathies. The proposed pathogeneses of TNF--associated neuropathies include both a T-cell and humoral immune attack against peripheral nerve myelin, vasculitis-induced nerve ischemia, and inhibition of signaling support for axons. Most neuropathies improve over a period of months by withdrawal of the TNF- antagonist, with or without additional immune-modulating treatment. Preliminary observations suggest that TNF- antagonists may be useful as an antigen-nonspecific treatment approach to immune-mediated neuropathies in patients with a poor response to, or intolerance of, standard therapies, but further studies are required.

Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:

1. recognize the important role tumor necrosis factor alpha plays in many aspects of immune system development, immune-response regulation, and T-cell-mediated tissue injury.
2. recognize tumor necrosis factor alpha in inflammatory neuropathies.
3. describe the potential of the treatment of neuropathy with tumor necrosis factor alpha blockade.

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INVITED REVIEW

ABSTRACT: Tumor necrosis factor (TNF-α) plays an important role in many aspects of immune system development, immune-response regulation, and T-cell–mediated tissue injury. The evidence that TNF-α, released by autoreactive T cells and macrophages, may contribute to the pathogenesis of immune-mediated demyelinating neuropathies is reviewed. TNF-α antagonists (infliximab, etanercept, adalimumab) are indicated for the treatment of advanced inflammatory rheumatic and bowel disease, but these drugs can induce a range of autoimmune diseases that also attack the central and peripheral nervous systems. Case histories and series report on the association between anti–TNF-α treatment and various disorders of peripheral nerve such as Guillain–Barré syndrome, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex, and axonal sensorimotor polyneuropathies. The proposed pathogeneses of TNF-α–associated neuropathies include both a T-cell and humoral immune attack against peripheral nerve myelin, vasculitis-induced nerve ischemia, and inhibition of signaling support for axons. Most neuropathies improve over a period of months by withdrawal of the TNF-α antagonist, with or without additional immune-modulating treatment. Preliminary observations suggest that TNF-α antagonists may be useful as an antigen-nonspecific treatment approach to immune-mediated neuropathies in patients with a poor response to, or intolerance of, standard therapies, but further studies are required.


TUMOR NECROSIS FACTOR-α ANTAGONISTS AND NEUROPATHY

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Cytokines are biologically active polypeptides released at sites of inflammation by a variety of cell types, ranging from T cells and macrophages to fibroblasts and astrocytes. Cytokines have stimulatory or inhibitory effects on the immune system, and can either synergize with one another or act antagonistically. Usually, there follows a cascade of cytokine secretion within the microenvironment of the responding T cells, so that one cytokine triggers the release of the next cytokine. Thus, responses of T cells are the result of the net effects of often antagonistic and competing cytokines released in the same microenvironment.

Tumor necrosis factor (TNF-α) plays an important role in many aspects of immune system development, immune-response regulation, and T-cell–mediated tissue injury. TNF-α is a cytokine with both pro-inflammatory and immunoregulatory properties and is involved in normal inflammation and immune responses. TNF-α is an important growth factor for prothymocytes and thymocytes, and thereby influences the generation of the T-cell repertoire. In the peripheral immune system, TNF-α plays important roles in antigen-presenting cell function, and in regulating apoptosis of potentially autoreactive T cells.

Two distinct receptors for TNF-α (p55 and p75) exist naturally as monomeric molecules on cell surfaces and in soluble forms. Biological activity of TNF-α is dependent upon binding to either cell surface receptor. The biological responses that are induced or regulated by TNF-α include expression of adhesion molecules responsible for leukocyte mi-
Tnf-α in inflammatory neuropathies

An important step in the pathogenesis of inflammatory demyelination is the invasion of the peripheral nervous system by activated, circulating, autoreactive T cells (Fig. 1). Homing and transmigration of these cells depend on the interaction of adhesion molecules, chemokines, and metalloproteinases. These neural antigen-specific T lymphocytes are locally reactivated, expand clonally, and release cytokines to orchestrate the subsequent immune response. TNF-α is released by these T cells or macrophages and acts at several stages in the development of inflammatory demyelination.

TNF-α can synergize with interferon-γ to upregulate the expression of recognition molecules [major histocompatibility complex (MHC) class II gene products and adhesion molecules] on antigen-presenting cells (macrophages and other accessory cells). Thereby TNF-α facilitates the initiation of a local immune reaction within the peripheral nerve. This cytokine exerts cytotoxic damage on vascular endothelium and a breakdown of the blood–nerve barrier that results in increased vascular permeability, which facilitates access to the nerve microenvironment of circulating factors such as immunoglobulins, cytokines, and complement. TNF-α can stimulate local macrophages to enhance phagocytosis.

**FIGURE 1.** Schematic representation of the basic principles of the cellular immune response of inflammatory neuropathy: autoreactive T cells (T) recognize a specific autoantigen presented by major histocompatibility complex (MHC) class II molecules and the simultaneous delivery of costimulatory signals on the cell surface of antigen-presenting cells, such as macrophages (Mφ), in the systemic immune compartment. Activated T lymphocytes then cross the blood–nerve barrier (BNB) to enter the peripheral nervous system (PNS). Here, T cells activate macrophages that enhance phagocytic activity, production of cytokines, and the release of toxic molecules, such as nitric oxide (NO), matrix metalloproteinases (MMPs), and pro-inflammatory cytokines, promoting demyelination and axon loss. The termination of the inflammatory response is facilitated, in part, by macrophages that induce T-cell apoptosis and release of anti-inflammatory Th2/Th3 cytokines, such as interleukin-10 (IL-10) and transforming growth factor-β (TGFβ). Reproduced from Kieseier et al.
cytosis and to release potentially injurious inflammatory mediators such as reactive oxygen and nitrogen oxide metabolites, complement, and proteases. Based on its myelinotoxic properties, TNF-α may represent a major noxious molecule by which macrophages, the chief effector cells of the immune response in Guillain–Barré syndrome (GBS), damage peripheral nerve. TNF-α also causes selective cytotoxic damage to Schwann cells and myelin sheaths. This inflammatory mediator could, short of inciting tissue damage, cause physiological changes by interfering with impulse propagation through changes in ionic channel expression.

Clinically, a pro-inflammatory role for TNF-α is supported by an elevated serum level in 27%–63% of patients with GBS, in 25%–57% of patients with chronic inflammatory demyelinating polyneuropathy (CIDP), and in 68% of patients with multifocal motor neuropathy (MMN). Serum levels correlated with disease and electrophysiological severity in some studies, and decreased after immune therapy and in parallel with the clinical recovery of patients. In GBS, this decrease occurred with a concomitant increase of soluble TNF receptors and IL-10, suggesting that the downregulation of pro-inflammatory cytokine production is associated with an increased anti-inflammatory response. This temporal association points toward the relevance of TNF-α in peripheral nerve demyelination in GBS/CIDP. However, it has not been determined whether the serum soluble TNF-α concentration reflects the activity of this cytokine in the nerve microenvironment.

By contrast, in a study of MMN, serum TNF-α levels increased transiently with clinical improvement after each intravenous infusion of immunoglobulins (IVIg). This increase may reflect an IVIg-induced shift from a presumed dominant anti-inflammatory antibody-mediated immune response toward a pro-inflammatory immune response. However, the pathogenetic relevance of TNF-α in MMN is unclear.

In patients with CIDP, high serum TNF-α levels correlated with electrophysiological evidence of demyelination diffusely distributed along the nerves. It was proposed that TNF-α disrupted the blood–nerve barrier and thus promoted demyelination in the intermediate nerve segments.

Furthermore, nerve biopsies of patients with CIDP showed that reactivated T lymphocytes exerted various effects by generating and releasing differentiation and proliferation signals, such as TNF-α and IFN-γ, or IL-2. Yet, it remains unproven that TNF-α is directly involved in the pathogenesis of CIDP, and this cytokine may merely be the result of activation of the immune system.

Experimental data demonstrated that intraneuronal injection of TNF-α produced predominantly axonal damage of sciatic nerve in mice. An immunocytochemical study in experimental autoimmune neuritis (EAN) showed that TNF-α–positive macrophages appear in nerve around the time of first clinical signs. As animals recovered, TNF-α immunoreactivity was no longer detectable. When animals with EAN received neutralizing monoclonal antibody to TNF-α, inflammatory demyelination was greatly diminished, and Schwann-cell apoptosis was reduced.

TNF-α may also be important in the development of pain states. Experimental application of TNF-α to nerves increased the background activity of C and Aδ fibers, and was noted to lower withdrawal latencies to mechanical and thermal noxious stimuli. Furthermore, anti–TNF-α neutralizing antibodies were observed to reduce thermal hyperalgesia and mechanical allodynia in two murine models of painful neuropathy.

**INDICATIONS FOR THE USE OF TNF-α ANTAGONISTS**

Elevated levels of TNF-α were detected in involved tissues and fluids of patients with various immune diseases. TNF-α inhibition represents a significant advance in the treatment of rheumatoid arthritis (RA), and is useful in the treatment of ankylosing spondylitis and psoriatic arthritis, as well as Crohn’s disease and ulcerative colitis. TNF-α blockers are indicated for: (1) reducing the symptoms and signs, improving physical function, and inhibiting the progression of structural joint damage in patients with moderate to severely active RA or psoriatic arthritis; (2) reducing symptoms and signs in patients with active ankylosing spondylitis; (3) reducing symptoms and signs, and inducing and maintaining clinical remission in adults and children with moderate to severely active Crohn’s disease who have had an inadequate response to conventional therapy; (4) reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adults with fistulating Crohn’s disease; and (5) reducing symptoms and signs, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderate to severe active ulcerative colitis who have had an inadequate response to conventional therapy.
Two classes of TNF antagonists are currently commercially available: soluble TNF receptor–Fc fusion proteins (etanercept) and anti-TNF monoclonal antibodies (infliximab and adalimumab). A schematic representation of the action of the drugs is depicted in Figures 2 and 3.

Infliximab (Remicade) is a chimeric IgG1-κ monoclonal antibody composed of human constant and murine variable regions. It is produced by a recombinant cell line cultured by continuous perfusion, and is purified by steps that remove and inactivate the virus. The molecular weight of the drug is about 149 kDa. Infliximab neutralizes the biological activity of TNF-α by binding with the soluble and transmembrane forms of TNF-α and thereby inhibits binding of TNF-α with its receptors.

Etanercept (Enbrel) is a soluble, dimeric fusion protein consisting of the extracellular ligand portion of the human p75 TNF receptor linked to the Fc portion of human IgG1. The drug is manufactured by recombinant DNA technology in a Chinese hamster ovary mammalian-cell expression system. It consists of 934 amino acids with an approximate molecular weight of 150 kDa. Etanercept inhibits binding of both TNF-α and TNF-β (lymphotoxin α) to cell surface TNF receptors, rendering TNF biologically inactive. The drug can also modulate biological responses that are induced or regulated by TNF-α.

Adalimumab (Humira) is a recombinant human IgG1 monoclonal antibody specific for human TNF-α.

**FIGURE 2.** Schematic representation summarizing similarities and differences between infliximab, etanercept, and adalimumab. Infliximab has mouse variable regions (purple) on both heavy and light chains linked to IgG1 constant regions (light blue). Etanercept contains the extracellular domain of human p75 TNF receptor (dark blue) and human IgG hinge and Fc domains (light blue). Adalimumab is a purely human recombinant IgG1 antibody (light blue). Multiple molecules of infliximab or adalimumab can bind a TNF trimer (yellow), but only one etanercept molecule binds TNF.

**FIGURE 3.** Schematic illustration depicting infliximab, etanercept, and adalimumab binding to cell-surface transmembrane (tm) TNF. Each molecule of infliximab or adalimumab may bind more than one molecule of monomeric or trimeric tmTNF; each tmTNF trimer can bind multiple molecules of infliximab or adalimumab. Etanercept probably binds to a single tmTNF, leaving one receptor binding site free. The variable region of infliximab is indicated in purple. The p75 TNF receptor portion of etanercept is indicated in dark blue. Both the heavy and light chains of human IgG1κ constant regions (infiximab), the human IgG1 hinge and Fc domains (etanercept), and the purely human recombinant IgG1 (adalimumab) are shown in light blue. tmTNF is shown in yellow.
The drug was developed using phage display technology resulting in an antibody with human derived heavy- and light-chain variable regions and human IgG-1 constant regions. The drug is produced by recombinant DNA technology in a mammalian-cell expression system and is purified by a process that includes specific viral inactivation and removal steps. It consists of 1330 amino acids and has a molecular weight of approximately 148 kDa. Adalimumab binds specifically with TNF-α and blocks its interaction with the p55 and p75 cell surface TNF receptors, and thereby modulates biological responses that are induced or modulated by TNF-α.

**DEFINITION OF DRUG-INDUCED ILLNESS**

Reports in the literature associate anti-TNF-α therapy with a variety of autoimmune diseases (systemic lupus erythematosus, a lupus-like syndrome, pally cutaneous vasculitis, and interstitial lung disease), central nervous system demyelinating disease, and peripheral neuropathy syndromes.48,55,60,74

According to proposed criteria, an illness (e.g., neuropathy) can be considered as drug-induced based on: (1) temporal association (manifestations of the illness occur after exposure and at a tempo consistent with the biological effects, mechanisms of action, and pharmacology of the exposure); (2) lack of likely alternative explanations; (3) stabilization/improvement of defining aspects of the disorder by interrupting exposure to the presumed inciting agent (more accurately, without addition of specific therapies); (4) rechallenge (reappearance/exacerbation of disorder after re-exposure to the inciting agent); (5) biological plausibility (the disorder is plausible based on known in vivo/in vitro mechanism of drug action); (6) analogy (similar disorders reported after similar exposure, e.g., central nervous...
system demyelination during anti–TNF-α therapy); (7) dose responsiveness (total dose of exposure related to development or severity of the disorder); and (8) specificity (manifestations of illness are the same or similar to previous cases exposed to the same drug or agent).

To report findings of a possible causal relationship between exposure and a clinical syndrome, at least 4 of the 8 attribution elements should be present. Based on these criteria, this report reviews only cases of peripheral neuropathy with a presumed association with TNF-α antagonism.

**PERIPHERAL NEUROPATHY ASSOCIATED WITH TNF-α ANTAGONISTS**

**Guillain–Barré Syndrome.** A postmarketing database, Adverse Event Reporting System (U.S. Food and Drug Administration), reported on 15 patients diagnosed with GBS in temporal association with TNF-α antagonist therapy (9 patients received infliximab, 5 received etanercept, and 1 received adalimumab).73 Electrodiagnostic studies (9 patients) were compatible with a peripheral demyelinating process. The interval was 6 weeks to 2 years between the start of drug infusion and onset of GBS. Reported antecedent events that may have played a role in the development of GBS included upper respiratory tract infections (3 patients), flu-like illness (2 patients), flu vaccine (1 patient), and fever of undetermined cause (2 patients). Possibly, therapy with TNF antagonists unmasked a latent infection or made patients susceptible to infection, thereby aggravating or inciting an autoimmune demyelinating process.60 Weakness evolved to an areflexic quadriparesis and neuropathies with electrophysiological studies compatible with a peripheral demyelinating process. The interval was 6 weeks to 2 years between the start of drug infusion and onset of GBS. Reported antecedent events that may have played a role in the development of GBS included upper respiratory tract infections (3 patients), flu-like illness (2 patients), flu vaccine (1 patient), and fever of undetermined cause (2 patients). Possibly, therapy with TNF antagonists unmasked a latent infection or made patients susceptible to infection, thereby aggravating or inciting an autoimmune demyelinating process.60 Weakness evolved to an areflexic quadriparesis and neuropathies with electrophysiological studies compatible with a peripheral demyelinating process. The interval was 6 weeks to 2 years between the start of drug infusion and onset of GBS. Reported antecedent events that may have played a role in the development of GBS included upper respiratory tract infections (3 patients), flu-like illness (2 patients), flu vaccine (1 patient), and fever of undetermined cause (2 patients). Possibly, therapy with TNF antagonists unmasked a latent infection or made patients susceptible to infection, thereby aggravating or inciting an autoimmune demyelinating process.60 Weakness evolved to an areflexic quadriparesis in 1 patient; 2 other patients required mechanical ventilation. Due to the limited information in some of the reports, it was unclear whether the resolution rates and outcome of postmarketing cases was different from other GBS cohorts. Furthermore, due to known underreporting in a postmarketing surveillance system, it is not certain whether the incidence of GBS during anti–TNF-α treatment is different from that in the general population.

**Miller Fisher Syndrome.** A patient developed a progressively worsening, relapsing–remitting ataxia and dysarthria that evolved into the Miller Fisher syndrome (ataxia, bifacial and bulbar palsies, partial ophthalmoplegia with nystagmus, areflexic flaccid quadriparesis) over 6 months while he received three successive infusions of infliximab.73 The serum GQ1b antibody titer was normal (<1:100). With immunomodulatory treatment, the patient recovered to unassisted ambulation over a period of months.

**Chronic Inflammatory Demyelinating Polyradiculoneuropathy.** Neurological symptoms and signs and electrophysiological studies compatible with CIDP were reported in 2 patients treated for variable months with etanercept or infliximab.3,59,66 Findings on nerve conduction studies suggested a demyelinating process and included conduction slowing, temporal dispersion of action potentials, and conduction block. Elevated serum anti-ganglioside (GM1 and GM2) IgM antibodies implicated a humoral component to the immune attack against myelin. The neuropathy improved after withdrawal of the drug.

Another patient was treated with infliximab and developed a polynuropathy with electrophysiological features of demyelination; her clinical response to IVIg was delayed, so that she deteriorated over 6 months before showing improvement.31 A sural nerve biopsy showed a disproportionate number of thinly myelinated fibers, mild axonal loss, a single onion bulb, and a single focus of perivascular mononuclear cells, but no active axonal regeneration, amyloid, or endoneurial inflammation.

The author investigated a patient with psoriatic arthritis who developed over several weeks a radial nerve palsy followed by an asymmetric motor polyneuropathy of the legs and trigeminal sensory neuropathy 4 weeks after the last of 10 infusions with infliximab (with a dosing schedule of 5 mg/kg every 8 weeks to 7 mg/kg every 5 weeks). Nerve studies showed a multifocal, predominantly motor, demyelinating polyneuropathy, without electromyographic evidence of denervation. Serum titers of co-asialo-GM1 autoantibodies were elevated (1:51,200), with normal titers against other monogangliosides, sulfatides, and myelin-associated glycoproteins. The patient improved slowly over a follow-up period of 9 months, and antibody titers normalized, after withdrawal of infliximab and several monthly courses of IVIg.

**Multifocal Motor Neuropathy with Conduction Block.** There are case reports of multifocal motor neuropa-thies with conduction block following treatment with infliximab.12,62,75,81 Patients developed asymmetric, progressive weakness; in 1 patient, weakness was reported to evolve over a relatively rapid 2-week period. Electrophysiological studies revealed conduction blocks of various motor nerves, with normal sensory nerve studies. There may be electromyographic evidence of an axonal component to this...
neuropathy. Serum anti-ganglioside (GM1) IgM antibody titers of patients were either elevated, normal, or not reported.

**Mononeuropathy Simplex or Multiplex.** A patient was reported with only sensory symptoms in a superficial peroneal nerve distribution after treatment with infliximab for 10 months. Electrophysiological studies confirmed an isolated peroneal neuropathy. Muscle biopsy showed Wallerian-like degeneration and mild neurogenic atrophy with no myelinated nerve fiber loss. An arteriole showed periarterial inflammatory infiltrate with partial obliteration of the lumen by fibrinoid necrosis. Another patient with symptoms of a sensory mononeuropathy multiplex suffered an extension of her neuropathic symptoms within hours after a first infliximab infusion. Neuromuscular biopsy showed a necrotizing vasculitis. A third patient had a transient ulnar sensory neuropathy followed 3 weeks later by a femoral neuropathy (12 weeks after remission of rheumatoid arthritis was induced by multiple infliximab infusions).

Nerve conduction studies showed an “acute” femoral nerve lesion.

**Axonal Sensory or Sensorimotor Polyneuropathy.** A patient treated with infliximab developed within months a small-fiber (painful) sensory symmetrical polyneuropathy (with normal electrophysiological studies). Two other patients developed a large-fiber sensorimotor polyneuropathy (mild decline of motor conduction velocities, loss of sensory nerve action potentials, and electromyographic evidence of denervation in the legs). The mechanism of nerve injury was a proposed “dying-back” neuropathic process.

**PATHOGENESIS**

**Guillain–Barré Syndrome and Miller Fisher Syndrome.** GBS comprises a heterogeneous group of conditions defined by varying clinical, electrophysiological, and pathological features. GBS can be considered an organ-specific immune-mediated disorder due to the synergistic interaction of cell-mediated and humoral immune responses to still incompletely characterized peripheral nerve antigens. The details of the pathogenesis of immune-mediated disorders of the peripheral nervous system were recently summarized elsewhere.

TNF-α probably has a pro-inflammatory function in the pathogenesis of GBS (serum levels correlate with disease activity and severity). TNF-α also has immunoregulatory functions. It suppresses T-cell reactivity to autoantigens in animal models of autoimmunity. TNF-α deficiency leads to failed regression of myelin-specific T-cell reactivity and prolonged survival of activated T cells. When endogenous TNF-α is blocked by repeated injections of a TNF-α antagonist, T-cell-proliferative responses and cytokine production are enhanced. The prolonged administration of TNF-α antagonists is thought to enhance autoimmune responses by altering antigen-presenting cell function, potentiating T-cell receptor signaling, and decreasing apoptosis of autoreactive T cells. 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 increases the risk of developing or prolonging an immune-mediated neuropathy. Therefore, TNF-α antagonist therapy could promote the development of GBS/MFS 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 GBS in immunogenetically susceptible patients.

**Chronic Inflammatory Demyelinating Polyradiculoneuropathy.** The presence of inflammatory infiltrates in the affected nerve suggests that disordered cellular immunity is involved in the pathogenesis of CIDP. A humoral role in the etiology has been attributed to antibodies, particularly anti-myelin and anti-Schwann-cell autoantibodies (Fig. 3). Emerging evidence points to gangliosides and other glycolipids as putative target antigens. The low frequency of specific antibodies observed in patients makes it likely that different antibodies and separate mechanisms are involved in different patients. A humoral immune component to the pathogenesis of CIDP associated with TNF-α blockade was supported in 2 patients by the presence of serum anti-ganglioside GM1 and GM2 IgM antibodies. Anti–TNF-α treatment probably induced a specific autoimmune response by increasing the number and activity of autoreactive T cells, thereby disturbing the equilibrium of the immune system, and thus provoked or exacerbated any deleterious pro-inflammatory and tissue damaging activities.
ropathy, the presumed pathogenesis was also an epitope-specific humoral immune attack against peripheral nerve myelin due to drug-induced immune system disequilibrium.

As the detected serum autoantibodies in reports are directed against different myelin components, it is likely that these demyelinating neuropathies result from a drug-induced nonspecific immune dysregulation and not from an attack against a cross-reacting epitope shared by a drug and a particular peripheral nerve antigen.

**Multifocal Motor Neuropathy with Conduction Block.**

MMN is a well-defined purely motor polyneuropathy characterized by the insidious progression of asymmetric weakness that develops over months to years, with symptoms sometimes persisting for decades before diagnosis. Diagnostic features include the presence of multifocal partial motor conduction blocks, frequent association with anti-GM1 IgM antibodies, and usually a good response to IVIg treatment.

Issues that remain to be clarified include the pathogenesis (including the role of anti-GM antibodies), its nosological position and relation to other chronic dysimmune neuropathies, and the existence of an axonal form of MMN. The current concepts and controversies pertaining to MMN were recently reviewed elsewhere.

An autoimmune etiology is supported by pathological findings of immunoglobulin deposition and inflammatory demyelination in motor roots (autopsy case); perivascular demyelination (motor nerve biopsy), and sensory nerve biopsies showed minimal involvement and no inflammatory changes. Antibodies directed against gangliosides are a marker of humoral immune involvement and may be pathogenic. High serum titers against GM1 (located at the axonal surface near the nodes of Ranvier) were found in 50% of all patients; other patients carried antibodies to GD1a. The role of cellular immunity remains unclear. Response to immunomodulatory treatment provides strong support for the autoimmune nature of MMN.

Based on this information, an immune mechanism was presumed in case reports of MMN temporally associated with TNF-α blockade. However, this association gives no further insight into the etiology of MMN or the mechanism whereby TNF-α inhibition triggers the immune attack. Alternatively, a possible ischemic mechanism was proposed for these "atypical" cases of MMN after infliximab treatment, based on: (1) the relatively rapid progression of the neuropathy; (2) the presence of cryoglobulins in a case report; (3) inconsistent presence of serum anti-GM1 antibodies; (4) the additional axonal electrophysiological features; and (5) the report of conduction block as a transient electrophysiological phenomenon at focal regions of axonal ischemia in vasculitic mononeuropathy multiplex, indicating that it is not synonymous with primary demyelination.

**Mononeuropathy Simplex or Multiplex.**

Neuromuscular biopsies showed necrotizing vasculitis. The temporal relationship between initiation of infliximab therapy and onset or progression of vasculitis suggests that TNF-α inhibition triggered or exacerbated vessel inflammation.

Autoimmune-like adverse events of the TNF-α blockers include leukocytoclastic vasculitis. Proposed mechanisms whereby TNF-α inhibitors promote (rheumatoid) vasculitis include: (1) development of anti-drug or autoantibodies during TNF-α blockade that form immune complexes that deposit in the walls of small blood vessels to activate complement and trigger a type III hypersensitivity reaction; (2) changes in T-cell cytokine production; (3) elevation of nuclear antigen levels in the blood due to increased apoptosis of cells targeted by TNF-α inhibitors; or (4) an increase in the immunogenic load due to downregulation of C-reactive protein by TNF-α inhibitors.

**Axonal Sensory or Sensorimotor Polyneuropathy.**

It has been suggested that constitutive TNF-α provides ongoing signaling support to peripheral neurons. Sequestration of TNF-α with inhibitors interrupts such transport to cause a “dying-back” type of axonal neuropathy. Although TNF-α may promote tissue regeneration in certain tissues (e.g., liver), it has no known regenerative effects in the central nervous system (CNS); it appears directly toxic to oligodendrocytes, and promotes demyelination.

**DOSE**

In different case reports, the timing of onset of neuropathy relative to the TNF-α inhibitor infusions varied considerably. Neuropathy started to worsen 8 hours after the first infusion (sensory mononeuropathy evolved to a sensory mononeuropathy multiplex), although onset of neuropathy started as late as 4 weeks after the third infusion (axonal sensory polyneuropathy).

The total duration of treatment before the onset of neuropathy varied from day 0 of the first infusion (sensory mononeuropathy multiplex) to 2 years.
(patients with GBS or MMN with conduction block). The reported infusion doses for infliximab were mostly at the standard recommended 3 or 5 mg/kg, but 1 patient was treated with 10 mg/kg.

The infusion schedule in patients who developed neuropathy varied from the standard induction regimen (weeks 0, 2, 6, and 14) to an interval of many months (e.g., four infusions in 2 years). The total number of infusions before onset of neuropathy varied from 1 to 12. The total dose administered before developing a neuropathy was not always reported, but varied from 540 to 1400 mg. In some case histories, the total exposure could not be ascertained as patients’ weights were not given.

TREATMENT AND PROGNOSIS

Withdrawal of Medication. On the assumption that TNF-α blockade triggered an immune attack against peripheral nerves, medication was discontinued in all the cases reported. Patients with CIDP, MMN, and axonal sensory and sensorimotor neuropathies improved spontaneously over follow-up periods of up to 9 months. Therefore, medication withdrawal is a prudent first step in the management of patients with suspected drug-induced neuropathy.

Corticosteroids. Intravenous methylprednisolone alone seemed insufficient as treatment for GBS, MFS, MMN, and vasculitic mononeuropathy multiplex associated with a TNF-α antagonist. Subsequent or concurrent treatment with intravenous cyclophosphamide or IVIg led to an improvement of neuropathy over follow-up periods of up to 9 months.

IVIg. According to established practice parameters, patients with GBS were treated with IVIg during the acute phase of the illness (11 of 14 cases; 2 not reported). The clinical outcome of patients varied from complete resolution of neurological deficits (within 3 weeks) to treatment unresponsiveness (follow-up period of up to 9 months). One patient with MFS was treated with IVIg, and recovered over 6 months from a flaccid quadriplegia to unassisted ambulation. Due to incomplete reporting of patient outcome, it is not clear whether the resolution rates or recovery of GBS associated with TNF-α blockade is different from GBS that occurs in the general population.

Maintenance infusions with IVIg for as long as 35 months resulted in improvement or recovery of neurological deficits in CIDP (1 patient), MMN (2 patients), and axonal sensory polyneuropathy (1 patient). However, based only on these case reports, it is not possible to conclude that IVIg definitively facilitated recovery.

Plasmapheresis. Three patients with GBS associated with TNF-α antagonists were treated with plasmapheresis alone, or with subsequent IVIg, so that neurological deficits partially resolved over follow-up periods ranging from 1 week to 9 months.

The prognosis of neuropathies appears generally favorable, so that most patients clinically improve by merely withdrawing the culprit drug. From previous case reports, it is not clear that immunomodulatory treatment is necessary or beneficial, except in patients with GBS and MFS, where IVIg or plasmapheresis remain the standard practice of care.

RE-EXPOSURE

A patient developed worsening ataxia and dysarthria 3–4 weeks after each of three infliximab infusions, and evolved into severe MFS over the course of 6 months. The neurological deficits improved after each exacerbation, either spontaneously or with methylprednisolone or IVIg.

Two patients with partially resolved GBS had recurrence of disease after each of repeated infliximab infusions. Two patients who recovered from GBS suffered no recurrence after rechallenge at 1 month (with infliximab) and 3 months (with etanercept), respectively. Another patient with a remote history of GBS (not drug-related) developed infliximab-associated GBS 3 months after onset of treatment. After IVIg, the patient recovered fully by 3 weeks, and was subsequently successfully rechallenged with lower dose infliximab at 3-month intervals.

With such limited reporting, no definitive conclusion can be drawn about the safety of TNF-α-blocker rechallenge once patients develop a neuropathy. Conceivably, lower drug doses could effectively treat the underlying inflammatory disease without altering the immune system enough to elicit a neuropathy.

TREATMENT OF NEUROPATHY WITH TNF-α BLOCKADE

Preliminary observations of a single retrospective, uncontrolled study suggested possible efficacy of etanercept treatment in selected patients with CIDP, or its variants, who were refractory to or intolerant of conventional therapies such as IVIg, plasmapheresis, or corticosteroids. Patients received a standard dose of etanercept at 25 mg subcutaneously twice weekly. Of 10 patients treated, 3 had significant im-
provement and 3 others had possible improvement as assessed by manual muscle strength testing, somatic thresholds, and functional disabilities 4–6 months after starting treatment. One patient had complete resolution of weakness, another was able to discontinue prednisone, and another temporarily relapsed when etanercept was transiently withdrawn. Any benefit of treatment with etanercept was probably mediated by inhibition of the pro-inflammatory role of TNF-α in the pathogenesis of inflammatory demyelination neuropathies.26,27 By modulating cytokine activity, TNF-α antagonists have potential as an antigen-nonspecific treatment approach to inflammatory demyelination of the central and peripheral nervous systems. Targeted treatment is not yet feasible as there remains uncertainty about the relevant autoantigens in these conditions.26

This study has some limitations. An assessment of the full potential of anti–TNF-α treatment of immune-mediated neuropathies warrants a prospective, controlled, double-blind clinical trial not limited to patients who fail presently accepted standard treatment regimens.

In one case report, mononeuropathy multiplex (demyelinating and axonal) complicated active Crohn’s disease and was treated with a series of infliximab infusions.61 The manifestations of neuropathy improved clinically after the first infusion, and after 22 weeks the electrophysiological studies returned to normal. The investigators were careful to suggest TNF-α blockade as a possible treatment option for patients with extraintestinal manifestations of inflammatory bowel disease. Moreover, a patient with rheumatoid vasculitis developed a presumed ischemic mononeuropathy of a common peroneal nerve, resistant to six infusions with cyclophosphamide and high-dose oral steroids, which resolved after six infusions of infliximab.2 This and other case reports and uncontrolled studies suggested that anti–TNF-α treatment is effective in the treatment of various types of systemic vasculitis. However, vasculitis is the most common autoimmune disease triggered by TNF-targeted therapies,21,56 so that treatment with these agents should probably be restricted to patients with vasculitis refractory to steroids and immunosuppressant agents.23 Meanwhile, one randomized, placebo-controlled trial showed no benefit of etanercept treatment for Wegener’s granulomatosis.92 Any benefits of TNF-α blockade will have to be weighed against the relatively mild drug side effects such as injection-site reactions (57%), upper respiratory tract infections (29%), and headache (17%), as well as the long-term safety concern of developing autoimmune processes (233 cases in 1 million patients treated).7,35

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