Demyelination and inhibition of tumor necrosis factor (TNF)

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ABSTRACT

The development of tumor necrosis factor alpha (TNFα) inhibitor therapy is arguably the most significant achievement in the treatment of rheumatic diseases to date. One serious potential side effect associated with these agents is the onset of neurologic signs and symptoms. In this paper we will examine the relationship of TNFα antagonism and demyelinating disease. Reviewing early laboratory and animal models, we discuss the mechanism of TNFα in central nervous system (CNS) injury and repair. Two negative studies of TNFα inhibitor therapy in the treatment of refractory multiple sclerosis (MS) are considered.

From the manufacturers' clinical development programs and post-marketing adverse event reporting data, we report the current incidence of demyelinating symptoms associated with each of the commercially available anti-TNFα agents. Comparing these reports to the incidence of MS in society as a whole, we find the rate of new cases of neurologic disease in exposed patients is not different from the rate of expected cases. Finally we explore arguments that support and refute a potential biologic relationship between TNFα neutralization and demyelinating disease.

Introduction

Since 1998, three biologic agents that specifically target Tumor Necrosis Factor-alpha (TNFα) have been introduced for the treatment of autoimmune diseases, including rheumatoid arthritis (RA), polyarticular juvenile rheumatoid arthritis (JRA), Crohn's disease, psoriatic arthritis, and ankylosing spondylitis. Compared with traditional disease modifying anti-rheumatic drugs (DMARDs) the anti-TNF compounds offer improved efficacy, more rapid onset of action, and impedance of the structural damage that characterizes the autoimmune destruction of these diseases. Not unexpectedly, rare serious side effects have been associated with these biologic compounds.

Surveillance from the Food and Drug Administration's (FDA) Adverse Events Reporting System (AERS) has identified multiple case reports of central nervous system (CNS) demyelination in the setting of TNFα inhibition. Given the growing use of these agents in clinical practice, it is prudent to critically consider the association between drug and disease before assuming causality. Several options must be considered: (i) the use of these agents caused disease, (ii) the use of these agents unmasked latent disease, or (iii) the use of these agents and development of disease are coincidental (1).

Review of the literature concerning a possible pro-inflammatory and immunosuppressive role of TNFα in the CNS suggests a pleotropic role for this cytokine in the development of multiple sclerosis (MS). The aim of this paper will be to review the literature regarding the pathogenicity of TNFα in CNS disease, to analyze available case reports of new demyelinating disease/MS after exposure to TNF inhibitors, and to offer possible explanations for the relationship between TNF neutralization and demyelinating disease.

Pathogenicity of TNFα in CNS disease

Early pre-clinical studies

Tumor Necrosis Factor-alpha (TNFα), a cytokine that is secreted by microglia and macrophages in the CNS, has been studied as a possible mediator of cytologic damage in MS plaques for more than 15 years. In 1988, Selmaj *et al*. described that axons from tissue cultures incubated with TNFα exhibited regularly spaced "bubbling" of the myelin sheath; the myelin involved in these dilatations eventually degenerated and was phagocytosed by surrounding reactive astrocytes (2). These activated astrocytes demonstrated pathologic changes similar to the reactive gliosis that is

found in demyelinating diseases such as MS (3). In addition, CNS explants treated with TNFα demonstrated oligodendrocyte necrosis; prior to these experiments TNFα had been shown only to mediate lysis of malignant cells (2). It was postulated that the TNFα mediated myelin and oligodendrocyte damage found in these tissue cultures was reflective of the pathophysiology of MS plaques.

Given *in vitro* evidence that TNFα could selectively damage CNS tissue, Sharief *et al*. hypothesized an *in vivo* correlation of TNFα levels with demyelinating disease severity. This author found that patients with chronic progressive MS had significantly higher levels of TNFα in their CSF (but not in their serum) compared with stable MS or control patients ($p < 0.001$) (4). Cerebrospinal fluid levels of TNFα were correlated with severity of disease and the rate of neurologic deterioration. High levels were also predictive of poor prognosis at 24 months of follow-up. Elevated TNFα levels were not correlated with the presence of oligoclonal bands, intrathecal IgG synthesis, or leukocyte count in the CSF (4). The lack of CSF pleocytosis and normal serum levels of the cytokine both suggest that TNFα is produced locally by intrinsic CNS cells in patients with active multiple sclerosis.

Extrapolating from the apparent emerging role of TNFα in demyelinating disease, several investigators examined the effect of TNFα inhibition in murine experimental autoimmune encephalomyelitis (EAE), a well established model for human multiple sclerosis. EAE can be induced in mice by injecting an encephalogenic myelin protein. Autoreactive T cells that are specific for the protein component of the myelin sheath likely mediate the clinical, immunologic and pathologic features of EAE. Mice afflicted with EAE develop tail weakness, hind limb weakness and cerebellar ataxia, symptoms similar to those experienced by humans who have MS (5). Examination of affected CNS tissue reveals infiltrating mononuclear inflammatory cells and widespread demyelination.

In early experiments, Selmaj *et al*. injected EAE-sensitized mice with a polyclonal anti-TNFα antibody preparation and compared results to control mice (5). None of the mice sensitized for EAE and subsequently treated with anti-TNFα antibodies developed inflammatory demyelinating disease. By contrast, the control mice showed clinical and pathologic signs typical of EAE. Unfortunately, the therapeutic response was not sustained. Upon cessation of polyclonal anti-TNFα antibody treatment, all study mice developed clinical signs of EAE within 5 to 7 days.

More compelling results were described with use of a monoclonal antibody to TNFα in EAE sensitized mice. Not only did treatment prevent development of EAE, but the monoclonal antibody therapy exhibited sustained effect up to 5 months after cessation of treatment (6). Similar experiments confirmed a similarly long-lasting treatment effect with the use of a soluble TNFα 55kd receptor (7).

Other investigators used transgenic mice to demonstrate the influence of TNFα in demyelinating disease. Probert *et al*. created mice that constitutively expressed a murine TNFα transgene in such a manner that this cytokine was over-expressed exclusively in CNS tissue. These TNF transgenic mice spontaneously develop severe progressive demyelinating disease by 8 months of age. Administration of a monoclonal anti-TNF antibody reversed the neurologic disease activity in severely afflicted mice and prevented the development of MS-like symptoms in the neonatal transgenic mice (8).

Later pre-clinical studies

Despite the data that TNFα is an important component of immune-mediated demyelination, a precise role for TNFα in the pathogenesis of MS remains unclear. In an elegant series of experiments, Liu *et al*. immunized a population of homozygous TNFα knockout mice and normal littermate controls with recombinant myelin oligodendrocyte glycoprotein (rMOG) to induce MS-like disease (9). Surprisingly, the TNF-deficient mice displayed profound neurologic impairment and high mortality. Histological evaluation of central nervous system (CNS) tissue revealed extensive demyelination and monocytic cell infiltration. Conversely, treatment of the TNFα knockout mice with recombinant TNFα dramatically reduced disease severity in afflicted mice and prevented development of a clinical MS-like syndrome in pre-treated mice. These studies suggested that TNFα may be protective of the CNS during the development of demyelinating disease and may serve to limit the extent of immune-mediated inflammation.

Another model for relapsing-remitting MS utilized the neurotoxin Cuprisone administered orally to knockout (TNFα -/-) and wild type (TNFα+/+) mice. Cuprisone predictably causes demyelination during dietary exposure and prompt remyelination occurs within one week following its removal (10). The wild type mice displayed more rapid and complete demyelination than the knockout mice when exposed to Cuprisone. However, upon removal of the neurotoxin, the wild type mice achieved > 80% remyelination compared to < 15% repair in the knockout cohort (11). These studies illustrate that while TNFα accelerates the process of acute demyelination, its presence in the CNS may be necessary for remyelination to occur.

To further understand the mechanism by which TNFα is responsible for disease and repair, the authors examined the roles of the two soluble TNFα receptors (55kd-TNFR1 and 75kd-TNFR2) and their effect on CNS progenitor cell proliferation. Only the TNFR2-/- mice displayed deficient remyelination, while the TNFR1-/- mice were indistinguishable from the wild type (TNFα +/+) controls. They further demonstrated that TNFα-/- and TNFR2-/- animals exhibited a significant reduction in the numbers of oligodendrocyte progenitor cells. The authors concluded that "TNFα signaling through TNFR2 promotes the accumulation of proliferating oligodendrocyte progenitors, which then develop into mature oligodendrocytes required for remyelination." (11).

Clinical trials in MS

By the late 1990s, several TNFα neu-

tralizing compounds were available for study in human disease. Multiple studies indicated significant improvement in the disease activity of patients with rheumatoid arthritis (RA) and Crohn's disease treated with anti-TNFα agents. Pre-clinical trials in MS suggested that TNFα was also a key effecter in immune-mediated demyelination. Although the role of TNFα in demyelinating disease was still under intense investigation, it was logical that these anticytokine agents merited study in human subjects with MS.

In a phase I open label study, 2 patients with rapidly progressive MS were treated with intravenous infusions of a chimeric monoclonal anti-TNFα antibody (infliximab; previously known as cA2) (12). Prior to study entry, both subjects exhibited aggressive disease resistant to high dose intravenous corticosteroids. Both patients experienced an increase in the number of gadolinium enhancing lesions on MRI, and increased CSF leukocytes and IgG index after each infusion. However, no clinically significant neurologic deterioration developed, and these values returned to baseline levels after 2-3 weeks.

In a phase II multicenter study, 168 patients with relapsing-remitting and secondary progressive MS received monthly infusions of lenercept (a recombinant soluble TNFR1 fusion protein) at three dose levels or placebo for up to 48 weeks (13). Pre-clinical data had convincingly shown that TNFα neutralization by lenercept prevented and treated active EAE in Lewis rats (14). The phase II study revealed no significant difference in the cumulative number of new active lesions on MRI (primary endpoint). However, lenercept treatment significantly increased MS attack frequency ($p = 0.0006$), although it had no effect on attack duration ($p = 0.62$) or attack severity ($p = 0.37$). The effect on attack frequency was most pronounced at the two higher doses employed. Antibodies against lenercept were generated in a majority of patients; they did not interfere with neutralization of TNFα but did hasten drug elimination (15). The trial was halted at 24 weeks due to these significant adverse outcomes.

Define the problem: Case reports from 3 anti-TNFα biologic agents

Although TNFα inhibition in trials of MS were unsuccessful, biologic therapies directed against TNFα have revolutionized the treatment of RA, Crohn's disease, JRA, and are increasingly being utilized in psoriasis/psoriatic arthritis (PA) and ankylosing spondolytis (AS). It is estimated that more than 500,000 patients have been or are currently undergoing treatment for autoimmune disease with TNFα antagonists. Although anti-TNFα therapies have proven to be among the most efficacious disease modifying anti-rheumatic drugs (DMARDs) available, clinical trial and post-marketing reports of serious adverse events highlight the need for vigilance when using this agents.

With increasing utilization of TNF inhibitors worldwide came increasing numbers of cases of demyelinating syndromes reported in patients receiving these therapies. Mohan *et al.* reported a series of 19 cases of neurologic events in patients treated with anti-TNF agents through December 2001 (16). Most (> 16) clinical reports of neurologic symptoms were associated with demyelinating lesions on MRI. Clinical signs and symptoms closely resembled features of MS and included optic neuritis, diplopia, cognitive disturbance, speech disturbance, paresthesia, weakness, incontinence, and Lhermitte's sign. The average time between the beginning of therapy and onset of symptoms was 5 months. Four patients had a prior history of MS and reported a flare of MS-like symptoms on exposure to the drug. Discontinuation of anti-TNFα therapy resulted in complete or partial resolution of the neurologic symptoms in all patients. Only one patient was re-challenged with the drug and subsequently developed worsening MS symptoms and MRI findings at four months; his neurologic deficits are reported to be permanent.

In the three years since the publication of Mohan's case series, significantly more patients have been treated with TNFα inhibition and a larger post-marketing experience has accrued. At the time of the writing of this manuscript (June 2004), three TNF inhibitors are commercially available for the treatment of autoimmune disease. In order to better understand the incidence of demyelination seen in association with TNF inhibition, we contacted each of the manufactures to report the number of events observed during the clinical development program and the number of adjudicated events reported as part of the post-marketing surveillance programs.

Demyelinating disease was suspected as a potential adverse event (AE) during the clinical development of each of the commercially available anti-TNFα agents. In the infliximab clinical development program, 2 cases of demyelinating disease were reported in 2,427 patients receiving the study drug as of September 2003 over 5,443 patient years. Both of these cases occurred in patients with Crohn's disease (Genovese MC: personal communication). In the etanercept clinical development program, two cases were reported in 3,839 patients over 8,336 patient years as of December 2002. Neurologic symptoms included one case of new onset MS in a patient with RA and one case of a relapse of MS in a patient with psoriatic arthritis (Genovese MC: personal communication). The adalimumab clinical development program at the time of FDA filing identified 4 cases of demyelinating disease in 2,468 patients over 4,870 patient years. One patient had a previous diagnosis of MS. Neurologic symptoms included optic neuritis and paresthesia. All 4 patients discontinued the anti-TNF therapy; 3 patients experienced complete resolution of symptoms, while one patient had residual paresthesias (Genovese MC: personal communication).

Review of the post-marketing data from each of these compounds offers additional information. As of August 2003, there have been 27 cases of demyelinating or MS-like syndromes seen in approximately 492,000 patients treated with infliximab. The types of neurologic symptoms were reported as demyelination, aggravation of MS, or MS-like syndrome (Genovese MC: personal communication).

As of May 2003, approximately 190,000 patients with 338,000 cumula-

tive patient years have received etanercept. There were approximately 15 new onset MS cases, approximately 13 new onset cases of optic neuritis, and an unknown number of cases of relapse or demyelination (Genovese MC: personal communication). As of December 31st, 2003 there were zero cases of demyelinating events reported with adalimumab out of an estimatated 16,869 patient years of experience (Genovese MC: personal communication).

On reviewing these data, several matters deserve mention. The clinical trials and post-marketing figures that we report may not be absolute numbers; because little information accompanies these data, it is likely that some cases are reported multiple times, some cases have not been reported at all, diagnostic criteria are not standardized, and the follow-up is frequently not known. It is also important to consider whether the demyelinating events reported are "true MS". Much data indicate that TNFα-antagonists exacerbate pre-existing MS (12, 13). However, the case reports we have reviewed suggest that many disparate neurologic signs and symptoms have been associated with anti-TNFα agents. It remains less clear that these biologic agents truly evoke MS or whether they comprise a variant autoimmune demyelinating process. Of greatest interest, however, is whether the cases of demyelination reported are occurring at a greater incidence than would be seen in the same population not using TNFα inhibition.

Burden of demyelinating disease

In order to better understand the incidence and prevalence of cases reported in both clinical trials and in post-marketing surveillance, it is important to examine the burden of demyelinating disease (i.e. MS) on the unexposed population. Recent prevalence estimates suggest that MS affects approximately 211,000 (± 20,000) people in the United States (US) (17). These data suggest that 85 people in a population of 100,000 would have pre-existing MS (17) and 6 people per 100,000 would develop new onset MS each year (18). Most studies agree that women are 2-3 times more likely to suffer from demyelinating disease (17). However, the prevalence of MS in the US varies considerably between geographical regions. For example, the lowest burden of disease in the southern states of the USA (17,18). Although several studies report a trend toward increasing incidence, these data may be biased by diagnostic changes, for example more widespread use of MRI. Also, a trend toward increasing prevalence could be explained by better treatments, resulting in longer survival of patients and hence prolonged duration of disease (17).

Genetic and environmental factors are commonly implicated in the pathogenesis of MS and other autoimmune diseases. Strong evidence suggests a familial or genetic component. A first degree relative of a MS patient has 20-40 times excess risk of developing disease compared to the general population (19). Among monozygotic twins, the concordance rate is 31% versus only 5% among dizygotic twins (20). Much research has been dedicated to describing the genetic blueprint that defines MS. Other than the increased risk conferred with expression of the HLA-DR2 allele, no candidate gene or region is linked to the development of MS (18). Therefore, most experts believe that environmental exposures are important in the expression of disease. The variation in MS frequency around the world suggests an environmental component. The lifetime risk of MS increases after migrating from a low risk to a higher risk area (21). One could hypothesize that MS occurs in persons genetically susceptible to immune disregulation who are exposed to an undefined environmental stimulus.

Acknowledging the disturbance of immune function in patients with MS, it is reasonable to suspect that these patients, and their families, are prone to develop other autoimmune diseases. Autoantibodies are more frequent in MS patients than in healthy controls (22). Seropositivity for antimyelin antibodies is associated with an increased risk for relapsing-remitting MS (23). Several sources suggest that other autoimmune diseases are associated with MS. In a hospital-based case-control study of 155 patients with MS and 200 controls, MS patients had a statistically significant higher coexistence of RA, psoriasis, and goiter than matched controls (OR = 2.96, 95% CI 1.23–7.66) (24). Moreover, a family history of autoimmune disease is common in patients with MS. Heinzlef reported that 15% of French MS patients have a first degree relative with autoimmune disease (25).

The excess risk of MS associated with environmental exposures, genetic susceptibility, increased autoantibody production, and family history illuminates a predisposition to autoimmune disease. This increased genetic predisposition is likely conferred by non-MHC genes, as MS, RA and Crohn's are associated with different MHC alleles. Nevertheless, the cohort of patients with RA and Crohn's disease who develop neurologic signs after exposure to TNFα inhibitors may innately be at increased risk of developing MS over the general population.

Theories to explain the possible relationship of TNF α inhibition and demyelinating disease

While it is difficult to establish a causal relationship between TNF inhibition and the development of demyelination, several features suggest a correlation. The timing of the adverse event following exposure to therapy suggests a temporal association between drug and event. In most cases, neurologic signs and symptoms resolved following discontinuation of therapy. On re-challenge, some patients experienced recurrence of symptoms. However, not all patients who have been re-challenged have experienced symptoms of demyelinating disease (Genovese MC: personal communication).

Several theories have been postulated to explain a potential biologic relationship between TNF neutralization and demyelinating disease:

1. "Lack of entry" hypothesis (26)

The CNS is uniquely protected from changes in the environment by the blood brain barrier (BBB). This network of tight junctions between brain capillary endothelial cells prevents entry of inflammatory cells, microbes, and macromolecules into the CNS (27).

Transport of drugs across the BBB is limited to lipid soluble small molecules with a molecular mass under 400-600 Da (28). Infliximab was not detected in the CSF of the two rapidly progressive MS patients with RA nor in RA patients who received anti-TNF treatment (12). Other biologic molecules are notably absent from the CNS likely due to size and lipid composition. While this lack of entry hypothesis could explain the failure of the TNF inhibition in clinical trials of active MS, it does not adequately explain the occurrence of new or worsened demyelinating symptoms in RA or Crohn's patients receiving anti-cytokine therapy.

2. Increase in peripheral T-cell autoreactivity (26)

Increasing evidence from animal models suggests that exposure to TNFα alters T-cell reactivity. Cope *et al*. used non-obese diabetic (NOD) mice to demonstrate that prolonged exposure to TNFα resulted in decreased T-cell proliferation and cytokine production; conversely, TNFα inhibition unregulated lymphocyte activity (29). Specifically, the authors reported that anti-TNFα therapy administered to adult NOD mice inhibits T-cell apoptosis, increases antigen presenting cell (APC) function and increases T-cell signaling. These results suggest that chronic TNFα inhibition may actually increase the T-cell response to a specific antigen (29).

It is well established that synovial membranes (in RA) and intestinal mucosa (in Crohn's disease), tissues that are readily penetrated by TNFα antagonists, demonstrate local TNFα inhibition and decreased joint and bowel wall destruction when exposed to these agents (30). However, cavities that restrict the entrance of TNFα antagonists display an overall increase in lymphocyte production with concomitant increased cytokine production of both Th1 (IL2, INFγ) and Th2 (IL4, IL10) lineages (29). Therefore, it is possible that peripheral administration of anti-TNFα agents has more than one effect: (1) local anti-inflammatory effects in tissues with adequate drug penetration, (2) systemic pro-inflammatory effects in tissues protected from drug entry. In this manner it is plausible that TNFα antagonists upregulate the autoimmune response by increasing T-cell effector function in the protein/macromolecule-restricted CNS while decreasing the joint and mucosal inflammation in patients with RA and Crohn's disease.

3. Alteration of downstream cytokine production (13)

As the chief effectors of intercellular communication, cytokines regulate the immune system by a complex network of positive and negative feedback loops. TNFα mediates both pro-inflammatory and anti-inflammatory effects through downstream cytokine production. Signaling through TNFR1 and TNFR2 activates nuclear factor-β to stimulate production of IL-1, IL-6, IL-8, IL-10 and PGE2; in this way, TNF modulates epithelial cell barrier permeability, expression of adhesion molecules, and recruitment of inflammatory cells (31). The production of IL-10 and PGE2 results in inhibition of cytokines IL-12 and INFγ (13). The cytokine profile of patients with active MS is well characterized: decreased IL-10 and increased IL-12 are associated with high MS disease activity (32). A randomized study of 18 patients with relapsing-remitting MS found that INFγ provoked MS attacks (33). Therefore, it is possible that inhibition of TNFα and its downstream mediators may result in decreased IL-10 and increased IL-12 production and create a cytokine profile that is associated with worsened demyelinating disease activity.

4. Role of TNFα in remyelination (11)

The notion that TNFα is a critical factor in immune-mediated demyelination has been well validated in multiple animal models. Hypothesizing that this cytokine may also be involved in tissue repair, Arnett *et al*. demonstrated that TNFα signaling through TNFR2 was necessary for the proliferation of immature oligodendryocytes (11); once mature, these cells brought about remyelination and repair of damaged axons. Compared to mice lacking TNFα, wild type mice experienced nearly complete repair of immune mediated myelin damage. These experiments were the first to suggest that TNFα may have a dual role in the pathogenesis of relapsing-remitting MS lesions. Like the TNFα deficient mice, it is reasonable to believe that therapeutic inhibition of TNFα (if it crosses the blood brain barrier) may prevent the repair of previously innocent axonal injuries and foster myelin damage.

5. Unmasking latent infection (26)

One important immunologic role for TNFα is its ability to contain infection through granuloma formation. Animal studies have shown that TNFα is critical for localizing and preventing reactivation of latent mycobacterium tuberculosis infections (34). Keane *et al*. reported a markedly increased rate of tuberculosis in patients treated with infliximab compared to background rates and suggested that TNFα was a key contributor to control of latent infections (35). It is conceivable that decreased TNFα activity could unmask an unnamed latent infection critical to the development of MS, inciting an autoimmune demyelinating process.

Several factors argue against a true association between demyelination and exposure to anti-TNFα therapy

1. Burden of MS to society as a whole

The background rate of MS in society as a whole is approximately six new cases per 100,000 per year (18). The rate of new cases of MS reported in post-marketing surveillance with each of the three TNFα inhibitors is at or below the number of expected cases based on the background rate for society. Given the small number of new cases of MS reported thus far in association with TNFα inhibition, the likelihood of exposed patients to develop MS may not be different than the unexposed population. It is possible that the association of demyelinating disease and anti-TNFα therapy is purely a reflection of reporting bias.

2. Co-existence of MS and autoimmune disease

Acknowledging the small study population and limitations of study design, Midgard (24) and others offer intriguing data that the incidence of chronic inflammatory disease is higher in patients with established MS than in a control population. Perhaps the cohort of patients who reported neurologic symptoms were predisposed to devel-

oping MS in the future regardless of anti-TNFα therapy exposure.

Conclusions

TNFα inhibition is arguably the most important achievement in the treatment of many autoimmune diseases in the past decade (34). The design of these biologic agents represents a sophisticated appreciation of the immune effector mechanisms that promote rheumatic disease. Defining the relationship between these revolutionary drugs and their adverse events represents a crucial step in our understanding of cytokine mediated illness.

The issue of drug therapy resulting in or being associated with an adverse medical event is an important clinical problem. Due to demands for patient safety, a suspected drug is frequently presumed to be at fault even in the absence of causal evidence. Physicians, pharmaceutical companies, and regulatory agencies must rely on surrogate criteria for assessing adverse drug reactions: (i) Did the reaction follow a reasonable temporal sequence? (ii) Did the patient improve after stopping the drug? (iii) Did the reaction reappear on repeated exposure? and (iv) Could the reaction be reasonably explained by the known characteristics of the patient's clinical state? (36).

Investigating the association of demyelinating CNS disease and TNFα inhibitor therapy is a formidable task. Although several theories have been offered to explain a possible relationship, all are flawed by lack of biologic plausibility or lack of supporting data. The case is complicated by an incomplete understanding of the role of TNFα in CNS damage and repair, conflicting literature reports in which cytokine inhibition improves demyelinating disease in animals but exacerbates MS in humans, a high frequency of MS in the background population, the unclear susceptibility to demyelinating syndromes in patients with chronic autoimmune disease, and imperfect reporting mechanisms for adverse drug events. While temporal correlation has been reported between TNFα inhibition and the development of demyelinating syndromes in a number of patients, the overall number of new cases reported does not appear to exceed what might be expected based on the incidence seen in the untreated population.

Despite this lack of clear association, vigilence is warranted. Patients with a history of MS, or MS-like illness are not good candidates for TNFα inhibition. Further, in the setting of TNF inhibition, should a patient develop new or unusual symptoms, TNF inhibition should be halted and appropriate evaluation pursued.

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