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REVIEW

Demyelinating and Neurologic Events Reported in Association With Tumor Necrosis Factor α Antagonism

By What Mechanisms Could Tumor Necrosis Factor α Antagonists Improve Rheumatoid Arthritis but Exacerbate Multiple Sclerosis?

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Introduction

Tumor necrosis factor α (TNFα) inhibition is the most significant advancement in the treatment of rheumatoid arthritis (RA) since the adoption of methotrexate in the 1980s (1,2). As TNFα antagonists have become increasingly utilized, both as monotherapy and in combination with traditional disease-modifying antirheumatic drugs, there have been a number of reports of demyelinating and other central nervous system (CNS) events in patients receiving TNF antagonists (3,4). It is unclear whether these cases represent coincidental events or whether they are side effects of the new therapies. If these events are side effects, then we need to identify the mechanism by which they are occurring. Because these agents are utilized with increasing frequency to treat a host of inflammatory and autoimmune diseases, there will undoubtedly be reports of drug associations and side effects. Careful examination of potential treatment-related adverse events is critical and may result in unique insights into the mechanisms of action of these novel therapeutic agents, as well as increase our understanding of the pathophysiology of the diseases currently being treated by these agents.

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Evidence of association between TNFα antagonists and demyelinating and CNS events

Recently, neurologic and demyelinating events have been reported in association with the use of TNFα antagonists in the treatment of RA and psoriatic arthritis. Various CNS events have been reported in patients taking etanercept, a p75 TNF receptor-immunoglobulin fusion protein, although the causal relationship with etanercept therapy remains unclear (3,4). As of November 2000 there were at least 9 cases of neurologic or demyelinating events reported in association with the use of etanercept (Siegel JN: personal communication). These adverse events could be broken into 4 general groups: 1) exacerbation/worsening of preexisting multiple sclerosis (MS), 2) new-onset MS, 3) acute mental status changes (encephalopathy) in which there was some residual deficit and/or evidence of demyelination on biopsy, and 4) cases in which the findings were consistent with neurologic disease but were not sufficient for the diagnosis of MS (such as optic neuritis, dysesthesia, and Lhermitte's sign) (Siegel JN: personal communication).

The clinical presentations of all of these cases varied greatly, and included altered mental status, dysesthesias, paresthesias, optic neuritis, or motor deficits. Many of the non-MS cases had clinical and/or radiographic features consistent with possible MS; it is possible that the primary association with TNFα antagonists is that they can cause exacerbation of autoimmune demyelination in patients with early MS (<2 exacerbations) or established MS. As of January 2001, 2 cases of neurologic events associated with magnetic resonance imaging (MRI) evidence of definite or possible demyelination have been reported in patients with RA in

association with infliximab use (Siegel JN: personal communication). Exacerbation of demyelinating disease appears to be associated with neutralization of TNFα rather than neutralization of lymphotoxin, since it has been seen in association with the TNF receptor fusion proteins lenercept and etanercept, which bind both TNFα and lymphotoxin, and also with the TNFα-specific antibody infliximab (5,6).

In MS, a T cell–mediated autoimmune disease similar to RA and Crohn's disease, there is evidence that TNFα antagonists do not provide clinical benefit and may, in fact, exacerbate disease (5,7). This is based on the adverse effects observed in 2 clinical trials involving the use of TNFα antagonists in patients with MS (5,7). Of the several agents designed to antagonize TNFα, only infliximab and lenercept have been directly studied in MS. In an open-label, phase I safety study, infliximab, a humanized mouse anti-TNFα monoclonal antibody, was administered to 2 patients with rapidly progressive MS (5). In both patients, infliximab treatment was associated with an increase in disease activity based on the appearance of new gadolinium-enhancing lesions on repeated MRI. Moreover, in a randomized, placebo-controlled, multicenter trial, a p55 TNF receptor–immunoglobulin fusion protein (lenercept) was studied in 168 patients whose MS fluctuated between periods of relapse and remission. Lenercept treatment was associated with an increase in MS disease activity as measured by the relapse rate ($P = 0.007$), with a trend toward more severe relapses and increased disease activity on MRI as compared with the placebo group (7).

Exercising caution before assuming causality

In a recent meta-analysis, it was estimated that MS affects ~160,000 people in the United States, with an incidence of 3.2 per 100,000 persons per year (8). Other reports have presented higher estimates, suggesting that MS affects from 250,000 to 350,000 people in the US and that the incidence is rising in certain regions of the US (9). Although certain autoimmune diseases are associated with a secondary autoimmune disease, to date no reports exist purporting either an increased incidence or prevalence of MS in the RA patient population. Based on these estimates and without correction for other factors, one would estimate that in a population of 100,000, 58 people would have preexisting MS and that 3.2 people would develop de novo MS each year. Although it is difficult to ascertain whether some of the demyelinating and other CNS events observed with TNFα antagonism represent de novo MS or another CNS process, it is possible that the majority of the TNFα antagonist–associated demyelinating and CNS events represent exacerbation of a preexisting state of early or established MS.

TNFα: a pleuripotent cytokine

TNFα plays a critical role in many aspects of immune system development, immune response regulation, and T cell–mediated tissue injury (10). TNFα has both proinflammatory and immunoregulatory properties (10–15). TNFα is a critical growth factor for prothymocytes and thymocytes, and accordingly influences generation of the T cell repertoire. In the peripheral immune system, TNFα plays important roles in antigen-presenting cell function and in regulating apoptosis of potentially autoreactive T cells (10).

Role of TNFα in T cell–mediated tissue injury in RA, Crohn's disease, and MS

TNFα is thought to directly drive the inflammatory cytokine cascade that activates metalloproteases and other degradative enzymes, thus leading to erosive joint destruction in RA, bowel tissue injury in Crohn's disease, and demyelination in MS (1,2,11,14–17). The central role of TNFα in driving tissue injury in RA and Crohn's disease is strongly supported by the therapeutic efficacy of TNFα antagonists (1,2,16). In MS, TNFα is detected in the cerebrospinal fluid, where its levels may correlate with disease activity (15,18). TNFα is found at high concentrations in MS brain plaques, causes oligodendrocyte cell death, injures the myelin sheath, and is implicated as a driving factor in demyelination (15,17–21).

Transgenic mice engineered to systemically overexpress TNFα develop erosive, symmetric polyarthritis and inflammatory bowel disease; these animal models share many of the clinical and histopathologic features of RA and Crohn's disease (11,14,22). Transgenic mice engineered to overexpress TNFα in the brain develop MS-like demyelination (15,23). In all of these examples, overexpression of TNFα causes localized tissue injury and results in arthritis, inflammatory bowel disease, or demyelinating disease in the absence of clear autoimmune responses (11,14,22,24). Several animal models of autoimmunity in which TNFα antagonists have discordant effects are discussed in detail below.

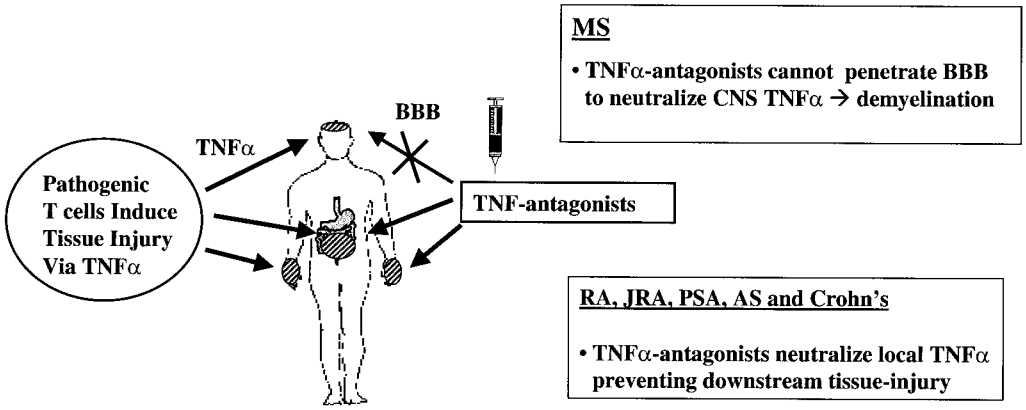

Figure 1. A proposed model for the dichotomous impact of tumor necrosis factor α (TNFα) antagonists on preventing tissue injury in rheumatoid arthritis (RA) and Crohn's disease as compared with multiple sclerosis (MS). For autoimmune diseases in which T cells infiltrate and mediate tissue injury, TNFα is produced and mediates tissue damage by driving inflammatory cytokine and degradative enzyme cascades. BBB = blood-brain barrier; CNS = central nervous system; JRA = juvenile rheumatoid arthritis; PSA = psoriatic arthritis; AS = ankylosing spondylitis.

Potential mechanisms for the discordant impact of TNFα antagonists in RA and Crohn's disease as compared with MS

Lack of entry of TNFα antagonists into the CNS. The observations presented above demonstrate that local TNFα plays a critical role in mediating tissue injury in autoimmune diseases including RA, Crohn's disease, and MS. These data suggest that TNFα could represent a central mediator of tissue injury in autoimmune diseases in which T cells directly infiltrate specific organs. The central role of TNFα in autoimmune T cell–mediated tissue injury is supported by the significant clinical benefit provided by TNFα antagonists in patients with RA and Crohn's disease (1,2,16).

The "lack of entry" hypothesis. In contrast to the joints and the bowel, the blood-brain barrier (BBB) makes the CNS an immune-privileged and protein-restricted site. Cerebrospinal fluid contains only 20–50 mg/dl of protein, which reflects prevention of entry of immunoglobulin and albumin (present in the serum at gm/dl levels) by the BBB. The BBB renders it highly unlikely that infliximab, lenercept, and etanercept are able to enter the CNS, wherein autoimmune T cell–induced TNFα mediates demyelination in MS. Even in active MS, cerebrospinal fluid protein concentrations are normal or only mildly increased. Thus, enhanced permeability of the BBB during active MS does not significantly enable entry of albumin, immunoglobulin, and, by inference, TNFα antagonists into the CNS. Infliximab was undetectable in the cerebrospinal fluid of the 2 patients in the previously described phase I safety study (5), even in the presence of active MS and BBB breakdown. Recombinant interferon-β (IFNβ) and interferon-γ (IFNγ), when delivered systemically, are undetectable in the cerebrospinal fluid (25–27). The lack of entry of TNFα antagonists into the CNS is a plausible explanation for their failure to attenuate TNFα-mediated demyelination in MS (Figure 1).

In humans with RA and Crohn's disease, appropriate dosing of the TNFα antagonist is critical to achieving an adequate clinical response. As described in the clinical trials for RA and Crohn's disease, when TNFα antagonists are underdosed, disease activity typically persists (1,2,16). This likely results from inadequate penetration of the joint and bowel tissues by the smaller doses of TNFα antagonists. The presence of naturally occurring soluble TNFα receptors and anti-TNFα antibodies complicates the measurement of recombinant TNFα antagonists in synovial fluid (28). In RA patients, significant amounts of systemically delivered anti-CD4 monoclonal antibody were detected in synovial fluid (29). Administration of infliximab to RA patients reduced TNFα synthesis by synovial cells (30). Based on these data, we predict that TNFα antagonists penetrate the joints in RA to neutralize local TNFα and reduce local TNFα production. In MS, because the BBB prevents entry of TNFα antagonists into the cerebrospi-

nal fluid, it is highly unlikely that therapeutic concentrations could be attained. This further supports "lack of entry" as a mechanism for the failure of TNFα antagonists to provide clinical benefit in MS.

A speculative mechanism by which TNFα antagonists enhance disease activity in MS via an increase in peripheral T cell autoreactivity. Although the lack of efficacy of TNFα antagonists in MS is explained by their inability to penetrate the BBB, this alone does not explain the worsening observed in MS patients (5,7). TNFα can induce both pathogenic and protective immune responses against self proteins (10–15). Systemic administration of TNFα antagonists enhances antigen-presenting cell function, increases T cell receptor signaling, and decreases apoptosis of potentially autoreactive T cells (10–14). Prolonged exposure to TNFα antagonists, either in vitro or in vivo, enhances the antigen-specific T cell responses (10,31). Long-term, systemic administration of TNFα antagonists to adult, nonobese diabetic (NOD) mice and (NZB $\times$ NZB)F_1 lupus mice enhances autoimmune disease activity (10,12–14). Thus, TNFα antagonists can increase the number and activity of autoreactive T cells, thereby enhancing autoimmune responses (10). This mechanism could explain how TNFα antagonists exacerbate MS disease activity.

In MS, interventions affecting the peripheral immune response alter disease activity in the CNS. Peripheral administration of IFNβ improves, while peripheral administration of IFNγ exacerbates, disease activity in the CNS (15,27). As discussed, it is unlikely that IFNβ and IFNγ achieve therapeutic concentrations in the CNS (25–27). IFNβ and IFNγ most likely exert a peripheral effect on the autoimmune response, which, in turn, modulates CNS disease activity.

In contrast to its minimal effect on entry of proteins, including TNFα antagonists and interferons, into the CNS, the inflammation and permeabilization of the BBB caused by active MS greatly facilitates entry of lymphocytes and other immune cells into the CNS. These cells can mediate and regulate autoimmune responses. Experimental autoimmune encephalomyelitis (EAE) is an animal model for MS. EAE is induced by injecting animals with an encephalogenic myelin peptide or protein in adjuvant, following which animals develop a demyelinating, relapsing, paralytic disease that shares many clinical, immunologic, and pathologic features with MS (15). EAE is mediated by autoreactive T cells specific for the protein components of the myelin sheath, and these activated autoreactive myelin-specific T cells enter the CNS and can subsequently exit and recirculate through the thymus and peripheral lymphoid organs (32,33). We propose that TNFα-antagonist treatment of MS could enhance activation and survival of peripheral autoreactive myelin-specific T cells, which subsequently could enter the CNS and provoke demyelination (Figure 2). The functions and mechanisms of action of TNFα are complex, and it is possible that TNFα antagonists may alter or increase peripheral autoimmunity by additional mechanisms.

In RA and Crohn's disease, TNFα antagonists penetrate joint and bowel tissues under autoimmune attack, and thereby neutralize and reduce production of local TNFα that otherwise would drive tissue injury. Even in the presence of a potential exacerbation of the specific autoimmune response, TNFα antagonists could control disease activity based on more powerful neutralization and reduction of production of local TNFα. The impact of TNFα antagonists on prevention of local TNFα-mediated tissue destruction could far outweigh the potential exacerbation of autoimmunity. When TNFα-antagonist therapy is discontinued in patients with RA or Crohn's disease, disease activity returns within weeks to months (1,2,16). Disease recurrence suggests that TNFα antagonists do not significantly attenuate the underlying autoimmune responses.

Based on the "lack of entry" hypothesis, intrathecal delivery of TNFα-antagonizing antibodies and fusion proteins is predicted to result in clinical benefit in MS. Small-molecule TNFα antagonists are under development. We predict that a small-molecule TNFα antagonist capable of penetrating the BBB might have a protective effect in MS.

Discordant results in animal models. Several animal models of human autoimmune disease exist in which TNFα antagonists have discordant effects. In contrast to their impact on MS, TNFα antagonists prevent and ameliorate EAE (15,34–37). The efficacy of TNFα antagonists in EAE could result from 1) dramatic disruption of the BBB in acute EAE (38), in contrast to the relatively minimal disruption inferred to occur in MS, or 2) use of much larger doses of TNFα antagonists relative to the human doses (34–37). In contrast to MS, in acute EAE, the BBB is disrupted to the extent that significant amounts of systemic immunoglobulin enter the CNS (38). This permeabilization of the BBB is likely to enable entry of TNFα antagonists, which, when delivered at high systemic doses, may result in therapeutic CNS levels that neutralize TNFα, thereby preventing demyelination. In separate experiments using TNFα-null mice, it was found that TNFα antagonists exacerbate, and TNFα ameliorates, EAE (39). These experiments are difficult to interpret because TNFα-null mice have

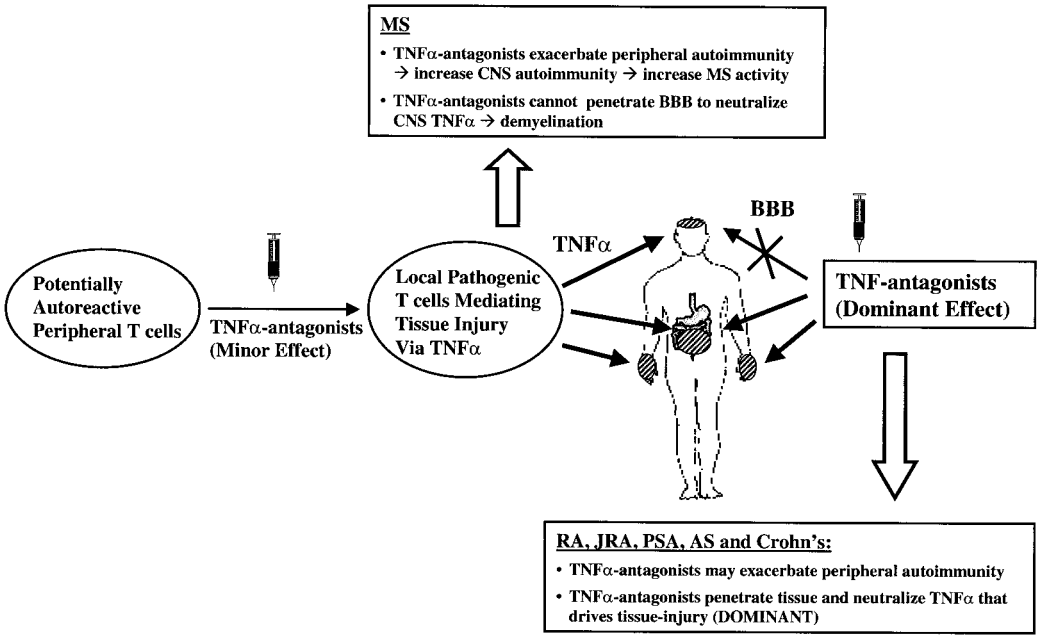

Figure 2. A proposed mechanism by which TNFα antagonists exacerbate MS by enhancing peripheral autoimmune responses. TNFα antagonists increase antigen-presenting cell function and inhibit apoptosis of potentially autoreactive T cells (9). Thus, introduction of TNFα antagonists results in increased numbers and activation of peripheral autoreactive T cells that could increase autoimmunity (9). In Crohn's disease and RA, TNFα antagonists penetrate tissues under attack and neutralize TNFα, thereby preventing tissue injury. In contrast, in MS, the BBB precludes entry of TNFα antagonists into the CNS. In MS, TNFα antagonists exacerbate peripheral autoimmunity, thereby increasing antimyelin autoreactivity in the CNS. Enhanced CNS autoreactivity in the absence of TNFα neutralization leads to increased MS disease activity. See Figure 1 for definitions.

significant abnormalities in lymphoid organ development, lymphocyte selection, and regulation of immune responses (10).

In adult NOD mice, a model for type I diabetes mellitus, TNFα antagonists worsen, and TNFα ameliorates, disease (10,12,14). Evidence suggests that the genetic background in NOD mice alters, and in some experimental systems reverses, the effects of TNFα on immune function and tissue destruction (12). The discordant data in NOD mice are difficult to interpret. In rodent models of systemic lupus erythematosus (SLE), discordant effects of anti-TNFα treatment also exist (10,13). Tissue damage in SLE is not directly mediated by tissue-infiltrating autoreactive T cells that induce TNFα production in a manner similar to that observed in RA and Crohn's disease. TNFα plays an important and complex role in rodent SLE. Although genetic background plays an important role in the discordant effects of TNFα antagonists in these rodent models, we do not have a clear understanding of the underlying mechanisms (10,13). These discordant results highlight the importance and complexity of TNFα's role in autoimmunity.

The sponge effect. TNFα antagonists could bind systemic TNFα (the sponge effect), thereby drawing local TNFα out of the joint and bowel tissues to provide clinical improvement in RA and Crohn's disease. The BBB would prevent TNFα from being drawn out of the CNS, and thus TNFα antagonists would not provide benefit in MS. As discussed, evidence suggests that TNFα antagonists may penetrate the joint and bowel tissue in therapeutic quantities to exert an effect at the local level. This could result in an overall reduction of TNFα in the body but relatively unchanged TNFα levels in the brain. Alternatively, this reduction of TNFα, or possibly the gradient developed across the BBB, could trigger an up-regulation of CNS TNF or TNF-receptor expression through a yet-unrecognized mechanism, further exacerbating TNF-mediated tissue injury in the CNS.

Heterogeneity of the role and mechanism of action of TNFα in diverse human autoimmune diseases. TNFα may not have the same importance in the pathogenesis of MS as it appears to have in RA and Crohn's disease. Perhaps TNFα is not the overriding mediator of demyelination in MS. TNFα could have a detrimental impact on RA and Crohn's disease, but a less dominant pathogenic, or even protective, impact on MS. Direct autoreactive T cell–mediated destruction could be a critical pathway in MS pathogenesis. Alternatively, TNFα antagonists could inhibit TNFα-induced interleukin-10 (IL-10) and prostaglandin E_2 production, resulting in increased IL-12 production which induces IFNγ expression (7); IFNγ exacerbates MS (27). The discordant effects of TNFα antagonists could result from disease-specific differences in the mechanisms of tissue destruction.

Potential role of TNFα in tissue regeneration. In certain tissues (for example, the liver), TNFα may foster tissue regeneration (40). An alternative mechanism for the detrimental impact of TNFα antagonists in MS could be inhibition of TNFα-mediated oligodendrocyte regeneration, thereby preventing remyelination. However, TNFα is not known to have regenerative effects in the CNS and the vast majority of evidence suggests that TNFα is directly toxic to oligodendrocytes and promotes demyelination (15,17–21). As discussed, TNFα antagonists are unlikely to enter the CNS in therapeutic concentrations. Thus, they would be unlikely to antagonize any currently unrecognized regenerative effects of TNFα in the CNS.

Unmasking latent infection. It is possible that therapy with TNF antagonists could unmask a latent infection, thereby aggravating or inciting an autoimmune demyelinating process.

Conclusion

Exactly why discordance exists in the effects of TNFα antagonism between different autoimmune diseases, all of which are believed to be mediated in part by TNFα, is unclear. A possible mechanism for the discordance of the efficacy of TNFα blockade in MS as compared with RA and Crohn's disease is the inability of TNFα antagonists to pass through the BBB to neutralize and prevent local TNFα-mediated tissue injury ("lack of entry"). Furthermore, systemic administration of TNFα antagonists can exacerbate autoimmunity by altering antigen-presenting cell function, increasing T cell receptor signaling, and decreasing apoptosis of potentially autoreactive T cells. TNFα antagonists could significantly increase the number and degree of activation of myelin-specific autoreactive T cells, thereby exacerbating autoimmune demyelinating disease.

Although the causal relationship between recently reported demyelinating events and currently available TNFα antagonists remains unclear, it seems prudent to avoid use of TNFα antagonists in patients with a history of demyelinating disease. Clinicians should exercise caution when considering use of TNFα antagonists to treat diseases in which autoimmune T cell–induced production of local TNFα has not been established to directly drive end-organ tissue injury, and in which safety and efficacy have not been demonstrated in human clinical trials. One cannot assume that because specific agents, in this case TNFα antagonists, have sound scientific rationale, supporting animal model data, and a beneficial impact on one human autoimmune disease that they will have similar beneficial effects on another human autoimmune disease. This paradox may be more frequently encountered in the coming years with the anticipated Food and Drug Administration approval of multiple biologic agents that modulate cytokine, chemokine, and costimulatory molecule function for the treatment of human autoimmune diseases.

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