Putting it all

From injection site and infusion reactions to more serious autoimmune disorders, here’s an evidence-based review of the immunologic and hematologic AEs associated with anti-TNF therapy.
The popularity of tumor necrosis factor (TNF-α) inhibitors has greatly increased across specialties due to their efficacy in treating immune-mediated disease. More than a million patients have received TNF-α inhibitor therapy with documentation of relatively high safety profiles. The US Food and Drug Administration (FDA) has approved etanercept for rheumatoid arthritis (RA), juvenile rheumatoid arthritis, ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis; infliximab for Crohn’s disease, RA, AS, PsA, and ulcerative colitis; and adalimumab for RA and PsA. In addition, there has been an increase in the number of evidence-based publications regarding their off-label use for cutaneous sarcoidosis, hidradenitis suppurativa, cicatricial pemphigoid, Behcet’s disease, pyoderma gangrenosum, multicentric reticulohistiocytosis, apthous stomatitis, Sneddon-Wilkinson disease, SAPHO syndrome (synovitis, acne, palmoplantar pustulosis, hyperostosis, and osteitis), pityriasis rubra pilaris, eosinophilic fasciitis, panniculitis/Crohn’s disease, necrobiosis lipoidica diabetica, dermatomyositis, and scleroderma.

However, these drugs have been associated with adverse events that have previously been reported in the literature. In our first installment we discussed reports on dermatologic conditions (e.g. leucocytoclastic vasculitis, interstitial granulomatous dermatitis, new onset of psoriasis, and non-melanoma skin cancer), hematopoietic malignancies, hepatotoxicity, and congestive heart failure. In our second installment we discussed infectious adverse events, including upper respiratory infections, tuberculosis, hepatitis B and C, HIV, and opportunistic infections. In this final installment we present an evidence-based review of the literature concerning immunologic and hematologic adverse events, including injection site and infusion reactions, multiple sclerosis, antibodies to TNF-α inhibitors, autoantibodies, drug-induced lupus, and hematologic toxicity.

**Injection Site and Infusion Reactions**

The development of antibodies against TNF-α inhibitors is responsible for injection site and infusion reactions, which commonly occur during the first minutes up to two hours after each infusion within the first months of therapy and diminish after successive administrations. Injection site reaction is the most common adverse event reported with etanercept and adalimumab, whereas infusion reaction is the most common for infliximab.

**Etanercept:** Etanercept produces an inflammatory reaction mediated by CD8+ T-cells. Symptoms range from mild to moderate erythema, pruritus, pain, or swelling at the site of injection. These local reactions can be treated with topical corticosteroids, moisturizers, and antihistamines. Type I hyper-
sensitivity reactions and anaphylaxis have also been reported following etanercept administration. Benucci et al reported two patients with RA who developed edema, erythema, and pruritus of at least 5-6 cm in diameter surrounding the injection site occurring six hours and five minutes, respectively, after the administration of subcutaneous etanercept. In both cases, positive immediate reactions were obtained and negative late readings in their respective intradermal tests with etanercept, suggesting an IgE-mediated immediate reaction. Two cases of urticaria-like lesions with prurigo developing bilaterally on the elbows after treatment with etanercept injections also have been reported.

Infliximab: The chimeric nature of infliximab is responsible for infusion reactions in 16-20 percent of patients with symptoms manifesting as fever, chills, headache, chest pain, and dyspnea. Patients often present with urticaria, labile blood pressure, serum sickness reactions, and anaphylaxis. Administering antihistamines and antipyretics before infliximab infusions can prevent or decrease the severity of these symptoms. Patients should be frequently monitored for up to two hours after the infusion.

Adalimumab: Common symptoms at the site of adalimumab injection include localized erythema, pain, pruritus, hemorrhage, and swelling, whereas rashes, nausea, headache, and abdominal pain are commonly reported as a result of adalimumab infusion. Approximately 19.5 percent of patients receiving adalimumab vs. 11.6 percent of those receiving placebo have been reported to develop mild to moderate injection site reactions, mostly attributed to pain (11.3 percent and 10.7 percent, respectively). Keystone et al reported injection-site reactions in similar proportions with adalimumab and placebo (24.1 percent and 24.0 percent of patients, respectively), again with pain as the most frequent reaction reported by 17 percent of adalimumab patients and 22 percent by the placebo group, whereas localized erythema, pruritus, or swelling occurred in only 6.2 percent of the adalimumab group and 3.0 percent of the placebo group (p=0.10). Type I, III, and IVb hypersensitivity reactions have also been reported following adalimumab administration. Type IVb hypersensitivity reaction is a Th2-mediated immune response where T cells secrete IL-4, IL-13 and IL-5 cytokines that promote B cell production of IgE and IgG4, inhibit macrophages, and recruit mast cells and eosinophils.

Multiple Sclerosis
TNF-α levels in cerebrospinal fluid are strongly correlated with multiple sclerosis (MS) activity and have been shown to be toxic to oligodendrocytes in vitro. Logically, TNF-α inhibitors were initially attempted as a treatment modality for MS but were abandoned due to failure of some clinical trials with patients having more frequent and severe exacerbations. Furthermore, there have been reports of new onset peripheral and central demyelinating disorders in patients taking TNF-α inhibitors for other inflammatory diseases. These reports have included MS, optic neuritis, transverse myelitis, and ascending motor neuropathy consistent with Guillain-Barré syndrome and have consequently led to warnings in prescribing instructions for etanercept, infliximab, and adalimumab. Additionally, individuals with a family history of MS appear to have an increased risk for developing demyelinating diseases associated with TNF-α inhibitors—17 with etanercept and two with infliximab.

As of 2001, the FDA has received 19 reports of demyelinating diseases associated with TNF-α inhibitors—17 with etanercept and two with infliximab.

Patients with symptoms of a central demyelinating disorder after TNF-α inhibitor therapy often have MRI evidence of new or increased multiple enhancing white matter lesions distributed throughout the brain and spine. Several studies have attempted to elucidate the underlying mechanism that triggers MS in some patients after TNF-α inhibitor administration. Andersson and colleagues studied blood and cerebrospinal fluid markers of inflammation in 10 patients...
with polyarthritis before and after treatment with infliximab. They detected an increase in systemic expression of interferon (IFN)-\(\gamma\), which is known to exacerbate multiple sclerosis. However, there were no signs of pleocytosis, oligoclonal immunoglobulin G bands, or increased IFN-\(\gamma\) in cerebrospinal fluid samples.\(^{50}\)

Robinson and colleagues outlined potential mechanisms for the discordant impact of TNF-\(\alpha\) inhibitors in RA and Crohn's disease as compared with MS. Their "lack of entry" hypothesis purports it is highly unlikely that TNF-\(\alpha\) inhibitors are able to cross the blood-brain barrier and enter the CNS to neutralize and prevent local TNF-\(\alpha\)-mediated tissue injury.\(^{51}\) Interestingly, over a decade earlier, van Oosten and colleagues found undetectable levels of infliximab in the cerebrospinal fluid of patients in a phase I safety study.\(^{52}\) Systemic administration of TNF-\(\alpha\) inhibitors may also exacerbate autoimmunity by altering antigen-presenting cell function, increasing T cell receptor signaling, and decreasing apoptosis of potentially autoreactive T cells.\(^{53}\)

Taking into account the limited clinical data available at this time, it is not possible to state with certainty whether TNF-\(\alpha\) inhibitors directly cause demyelination and CNS events. These CNS events may in fact represent unrelated de novo MS or the progression of previously subclinical MS. Additionally, MS may coexist with other autoimmune diseases that clinicians treat with TNF-\(\alpha\) inhibitors and merely represent a coincidence rather than causality.\(^{54,55}\) For example, Gupta and colleagues found demyelinating diseases to occur more commonly among patients with inflammatory bowel disease (IBD) than among non-IBD patients.\(^{56}\) However, taking into consideration the results of TNF-\(\alpha\) antagonists in MS patients and the number of associated cases of demyelinating events, we advise avoidance in patients with a personal or family history of demyelinating conditions and discontinuation in patients with new-onset neurologic symptoms until further studies are conducted.

**Antibodies to TNF-\(\alpha\) inhibitors**
The formation of neutralizing antibodies to TNF-\(\alpha\) inhibitors may lead to allergic infusion reactions, decreased efficacy, and requirements for higher and more frequent doses.\(^{57}\)

**Etanercept:** Etanercept is less immunogenic in comparison to other TNF-\(\alpha\) inhibitors and has no reports of the development of neutralizing antibodies following drug administration to date.\(^{58}\) There have been infrequent reports of non-neutralizing antibodies, which have not been demonstrated to affect the safety or reduce the efficacy of etanercept therapy.\(^{59}\) In one study of the long-term treatment of psoriasis with 50mg of etanercept administered twice a week, non-neutralizing antibodies were observed in 18.3 percent of patients.\(^{60}\)

**Infliximab:** Infliximab, with approximately 75 percent human and 25 percent murine components, generates a significant neutralizing human antichimeric antibody response against the murine component.\(^{57-66}\) Baert and colleagues compared the concentrations of infliximab and antibodies against infliximab in patients treated for Crohn's disease with a mean of 3.9 infusions per patient over a mean period of 10 months. They detected antibodies against infliximab in 61 percent of patients and found patients with antibody concentrations greater than 8.0mcg/ml to have a mean response duration of 35 days, as opposed to 71 days for patients with concentrations less than 8.0mcg/ml. Patients with infusion reactions also had significantly lower infliximab concentrations at four weeks and a shorter duration of clinical response.\(^{58}\) Due to the numerous drawbacks secondary to neutralizing antibodies, the FDA approved infliximab use only if administered in tandem with immunomodulators, such as methotrexate, 6-mercaptopurine, azathioprine, or corticosteroids, which could prevent the formation of anti-infliximab antibodies.\(^{58,67}\)

**Adalimumab:** Adalimumab is less of a concern, as the antibody is fully humanized. Despite this, there have been several reports of human antihuman antibodies (HAHA) in rheumatoid arthritis and Crohn's disease patients treated with adalimumab with one study demonstrating HAHA in 57 percent of patients with significantly increased serum levels in non-responders.\(^{58-71}\)

The issue of autoimmunity requires further study, as the mechanisms underlying a protein's immunogenicity are complex and poorly understood. Low pre-infusion serum levels of TNF-\(\alpha\) inhibitors may predispose individuals to the development of neutralizing antibodies. Adequate induction treatments of TNF-\(\alpha\) inhibitors, followed by maintenance treatment with intervals less than eight weeks, and monitoring with dose optimization may give stable serum concentrations in order to prevent formation of neutralizing antibodies and extend therapeutic benefits.\(^{58,62,66}\) Pitarch and colleagues transitioned eight patients with moderate-to-severe psoriasis to etanercept therapy after poor primary or secondary response with infliximab and found four patients to respond with decreased psoriasis area and improved PASI scores.\(^{72}\) This response to etanercept may be secondary to the ineffectivity of previously generated antibodies to infliximab on the new serum levels of etanercept. While this study is limited by its low power, clinicians may consider switching to etanercept after failure with other TNF-\(\alpha\) inhibitors.

**Autoantibodies and Drug-induced Lupus**
The development of antinuclear antibodies with TNF-\(\alpha\) antagonist use has been widely reported.\(^{73-77}\) Presence of
anti-dsDNA antibodies (eight to 15 percent of patients treated with infliximab, three to 15 percent treated with etanercept, and 5.6 percent treated with adalimumab) have also been reported to be related to TNF-α antagonist therapy.78 Gonnet-Gracia et al. found 43.6 percent of Rheumatoid Arthritis (RA) patients and 27.1 percent of Ankylosing Spondylitis (AS) patients to have significant levels of ANA at baseline; these percentages increased to 73 percent and 52 percent, respectively, after infliximab therapy.

Furthermore, the percentage of patients positive for anti-DNA antibodies increased from zero to 9.5 percent for RA, and from zero to two percent for AS, after infliximab treatment. Two patients developed chilblain lupus, possibly related to these auto-antibodies. However, in 229 patients with RA and AS, no significant changes in ANA, anti-DNA and C4 levels were observed after treatment with etanercept.79 Caramaschi et al. reported that 95 percent of RA patients treated with infliximab had a high ANA reading at least once during 12 months of therapy, as compared with only 37 percent before treatment, and at least half of these patients had a very high titer, greater than or equal to 1:1,280.80

Monitoring of antinuclear antibodies during TNF-α therapy is not currently recommended, as titers do not predict response, toxicity, or autoimmune events.83-84 The actual induction of a lupus syndrome is rare.81-83 Four cases of adalimumab-induced lupus have been reported.88-90 Patients who do develop a lupus-like syndrome usually reverse on cessation of the anti-TNF therapy. Furthermore, TNF-α inhibitor-induced lupus may be difficult to recognize due to its non-specific symptoms, and a high index of suspicion is required. Interestingly, there have been at least two cases in which the use of etanercept was associated with the disappearance of subacute cutaneous lupus erythematosus.90-91

The advent of anti-TNF-α therapy is an important advancement in the management of numerous inflammatory diseases, such as rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn’s disease, and ulcerative colitis. Hematologic Toxicities

Etanercept. Kuruvilla et al.92 reported a case of aplastic anemia complicated by sepsis in a patient taking etanercept for rheumatoid arthritis with resolution of pancytopenia three weeks after discontinuation of therapy. Additionally, Montané et al.93 reported a case of etanercept-induced neutropenia that was confirmed by two positive re-challenges. The mechanism of action of this adverse event is unknown, and a causal relationship has never been found. Etanercept’s drug label recommends caution in using the drug for patients with a history of blood dyscrasia. Physicians should be vigilant for signs of pallor, easy bruising, bleeding, or fever in patients undergoing TNF-antagonist therapy.

Infliximab. Neutropenia, thrombocytopenia, pancytopenia, agranulocytosis, and bone marrow toxicity have all been reported in patients after the initiation of infliximab therapy.93-97 As with etanercept, the mechanism of action is unknown; however, physicians should be aware of these rare but life-threatening adverse events with infliximab therapy.

Adalimumab: There is a paucity of reports documenting hematologic toxicity with adalimumab due to its recent FDA approval. Theodoridou et al.98 reported a case of new-onset T-large granulocyte lymphocyte proliferation and neutropenia after initiation of adalimumab therapy in a patient with RA.

The aforementioned hematologic toxicities are extremely rare and have mainly been mentioned in case reports. However, the physician must be aware of these complications, as prompt discontinuation of the agents can aid in resolution of the hematologic disorders.

Conclusion

Our goal with this three-installment review was to provide a comprehensive summary of recently published data through 2008 on the adverse events of TNF-α inhibitors. The advent of anti-TNF-α therapy is an important advancement in the
management of numerous inflammatory diseases, such as rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease, and ulcerative colitis. Reports about the safety of anti-TNF-α therapy have prompted cautious use due various risks, including risks of serious infection, congestive heart failure, malignancy, and multiple sclerosis, among others. This review emphasizes the need for appropriate pre-screening and systematic follow-up of patients receiving these drugs. Prescribing physicians should be aware of current concerns about the adverse events of the TNF-α inhibitors in order to ensure maximum efficacy and avoid serious medical complications.

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19. Simsek I, Erdem H, Pay S, Sobaci G, Dinc A. Optic neuritis occurring with anti-tumor necro-


