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HOTLINE
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Update on Safety Issues Concerning TNF Inhibitors

In the May 17, 2006 edition of JAMA a review/methodological paper was published that concerned the safety of TNF inhibitor antibodies (1). Little new information was presented in this review (see previous ACR Hotlines [2,3], and package inserts for these drugs). The story was widely distributed by the press, and caused concern among patients and prescribers of these agents. This ACR Hotline is offered to provide perspective and clarity regarding the safety of TNF inhibitors.

Even as the TNF inhibitors were first introduced into the clinic, rheumatologists were aware of the adverse effects that were possible with such potent immunomodulatory agents, in particular a greater propensity for infections and malignancies. With regular assessment by the FDA and other regulatory agencies, and with ongoing data from clinical trials, prospective registries and pharmacovigilance efforts, rheumatologists have gained insight as to the magnitude of the potential risks of treatment (4). Rheumatologists now realize that serious infections and certain malignancies such as lymphoma do occur, although rarely, in patients receiving TNF inhibitors, including those with RA. However, the extent to which other factors such as concomitant therapies, comorbidities, and the activity of RA contribute to the risk of these important side effects remains incompletely defined.

In the JAMA article (1) researchers from the Mayo Clinic reviewed available data from published articles on TNF blockade to better estimate the most serious of safety concerns, serious infection and malignancy. While all safety analyses on this important topic are welcome, the interpretations offered in this and other studies that combine distinct data sets should be tempered by consideration of inherent limitations in this approach.

1. This article reported higher rates of malignancies in patients treated with TNF inhibitors (29 of 3,493 or 0.8%) compared to those on either placebo or active controls (e.g., placebo + methotrexate) (3 of 1,512 or 0.2%). While the occurrence of malignancy was significantly different in the two groups, this serious toxicity remains rare in patients treated with these agents. Serious infections were reported in 126 of 3,493 or 3.6% of patients treated with TNF inhibitors and in 26 of 1,512 or 1.7% of controls. Data interpretation is complicated by factors such as the approach to characterizing time of exposure (the authors did not normalize their data for time of exposure).
2. These results are derived from combining patients in a meta-analysis. Clinicians should be aware there was considerable heterogeneity amongst patients included (e.g., early RA versus refractory RA, different concomitant therapies, variable comorbidities).
3. Some of the definitions used in defining groups are different from those used in clinical practice, such as the distinctions between “high and low doses” and “serious infections”.
4. While patients treated with etanercept were not included in this analysis, the spectrum of toxicities associated with all TNF inhibitors in previous analyses have been comparable (2,3). Toxicities are generally considered, for example by regulatory agencies such as the FDA, to be similar for all agents in the class.

The issue of lymphomas and TNF inhibitors has been extensively addressed (5). The question of what relationship there may be between solid tumors and TNF inhibitors has re-emerged. Database and registry data have consistently suggested that the risk of solid tumors among RA patients on TNF inhibitors is indistinguishable from the risks among the general population. However, several studies in specific populations have brought to light data suggesting there may be some risk. In a study of etanercept in patients with Wegener’s granulomatosis, all of whom had previously received treatment with cyclophosphamide, an excess of solid tumors was observed among patients receiving the TNF inhibitor (6). In a trial of infliximab in patients with severe COPD, an excess of solid tumors was observed among patients receiving the TNF inhibitor (7). Whereas increased malignancies (compared to the population) were not observed in RA or spondylarthropathy patients taking TNF inhibitors, an increase in lymphomas was observed, although at least part of this association seems to relate to disease activity (5).

INFLIXIMAB WARNING FOR HEPATOSPLENIC T CELL LYMPHOMA. The infliximab label was recently changed to include a new indication for pediatric Crohn's disease (CD). At the same time a new black box warning was added based on six reports of hepatosplenic T cell lymphoma (HSTCL). HSTCL is a rare and often fatal form of non-Hodgkins lymphoma that preferentially affects children and young adults, most of whom are transplant recipients receiving either azathioprine or 6-MP. Such patients manifest hepatosplenomegaly, fever, cytopenias, purpura, and elevated hepatic enzymes, usually without peripheral adenopathy. Six young adults (5 males, 1 female, ages 12-31 yrs.) were diagnosed with HSTCL after receiving 2 doses to 3 years of infliximab treatment for CD. There are no known reports of such events with etanercept or adalimumab; however, there has very minimal use of these other TNF inhibitors in this specific population (pediatric Crohn's). To date, no cases of HSTCL have been reported with the use of any TNF inhibitor in RA or juvenile arthritis.

The Bottom Line:

- The use of TNF inhibitors may be associated with an increased risk of infections, serious infections, and certain malignancies. While patients and rheumatologists should not be overly alarmed by the data presented in this recent article, the safety of antirheumatic medications is an important issue and discussion needs to continue between rheumatologists and their patients on this topic. As always, the potential risks of all treatments need to be balanced against the risks of uncontrolled active disease; and a wealth of data and clinical experience attest to the highly significant clinical effectiveness of the TNF inhibitors.
- Regarding infections, rheumatologists should continue to assess patients as regards their risks for infections when therapy with any of the TNF inhibitors is contemplated, to monitor patients assiduously for signs and symptoms of infection during therapy (including atypical infections), and to treat appropriately to prevent sequelae of infections should they occur.
- Reports of increased numbers of lymphomas in RA patients may relate more to the disease activity rather than its treatment. However, there may be an association between lymphoma and TNF inhibitors, and clinicians need to continue to assess patients for signs and symptoms of lymphoma. This report does not establish a new or increased risk of TNF inhibitor-related solid tumors. Moreover, this report does not examine whether it is safe to use these agents in patients with a prior history of malignancy. Clinicians must be aware of the risks of cancer among the patients they treat with immunomodulatory agents, for example based on their age, sex, exposures, comorbidities and other factors, and be vigilant for signs and symptoms suggestive of malignancy during therapy.
- Regarding hepatosplenic T cell lymphoma: all cases to date among patients on TNF inhibitors have occurred in those with Crohn's disease, all of whom had also received therapy with azathioprine or 6-MP. Nevertheless, rheumatologists ought to be aware of this very rare disease.

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American College of Rheumatology Hotline
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Information for Patients

Description
Biologics are new class of drugs that have been used since 1998 and have been studied for almost 10 years. Overall, they have been given to more than 800,000 people worldwide. “Biologic” drugs were developed based on the results of basic research over the last 25 years which identified proteins involved in the inflammatory process in the joints of patients with rheumatoid and other types of inflammatory arthritis. Biologic agents are genetically engineered drugs – meaning that human genes that normally guide the production of these natural human immune proteins (i.e., an antibody to TNF) are used to produce large amounts of a biologic drug. These drugs are given to decrease inflammation and swelling by interfering with substances in the body that cause or worsen inflammation.

Uses
Biologic agents have been approved by the FDA to treat moderate to severe rheumatoid arthritis. Because of their expense and side effects, most people with mild to moderate rheumatoid arthritis (RA) are treated with methotrexate before a biologic agent is used unless they are unable to take methotrexate because of side effects or other conditions. Biologic agents may be used alone, but are often given in conjunction with other DMARDs (e.g., methotrexate, leflunomide, azathioprine, hydroxychloroquine, sulfasalazine), to increase the benefit and limit potential side effects. When patients start biologic agents, they usually also remain on their current dose of nonsteroidal anti-inflammatory (NSAID) and/or corticosteroid (i.e., prednisone) medicines. Some of the TNF inhibitors have been approved for use in juvenile arthritis, Crohn’s colitis, psoriatic arthritis, ankylosing spondylitis, and psoriasis.

How it works
Four of the currently available biologic agents act as inhibitors of the cytokines IL-1 (anakinra (Kineret)) or TNF (etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira)). Cytokines are messenger molecules made by many of the body's cells that act to excite other immune system cells. Interleukin-1 (L-1) and tumor necrosis factor (TNF) are made in large amounts in rheumatoid arthritis and other forms of inflammation. In these diseases, TNF or IL-1 increases the inflammation in joints.

Two recently approved biologics are Abatacept (Orencia) and rituximab (Rituxan). Orencia interferes with the activation of T cells, an immune cell that promotes inflammation, and Rituxan depletes the body of B cells, which are also important in promoting inflammation. and damage.

Dosing
Biologic agents must be given by an injection under the skin (Enbrel, Humira, and Kineret)) or by intravenous (IV) infusion (Remicade, Orencia, and Rituxan). Patient education information and videos are available for the self injectable medicines. A nurse or physician can teach you about the medicine and how to give the injections. It often helps to bring a spouse or friend with you to learn how to do the injections. You can inject the medicine in the front of your thighs or abdomen. Injection sites should be rotated so that the same site is not used repeatedly. Most patients who fear self-injection are usually able to give these injections repeatedly with mild or no discomfort.
Remicade, Rituxan, and Orencia infusions are either done through an IV line in the doctor’s office or specialized infusion centers. These treatments usually take 1-3 hours, during which time the patient can rest, read, watch TV or do office work without discomfort.

Time to effect
Biologic agents usually work quickly to relieve the symptoms and swelling associated with rheumatoid arthritis. Although the studies show that most patients will improve within 4-6 weeks of treatment, most patients receiving Enbrel, Humira, or Remicade will notice marked improvement after the first or second injection. Rituxan and Orencia may take weeks to months to achieve their full effect.

Side Effects
Injection site reactions: The most common side effects seen with the injectable medicines include skin reactions, which are called “injection site reactions.” Skin reactions to injection occur in less than 30% of patients, and

such patients usually complain of localized rash, burning, or itching at the site of injection. With Enbrel and Humira these skin reactions may last up to a week. Kineret injection skin reactions may last for 10-14 days before fading away without a scar.
Infection: The most significant side effect of these medications is an increase in the risk of all types of infections, including tuberculosis (TB). Before starting Orencia or an anti-TNF medication, a TB skin test is usually done. Reactivation of hepatitis B has been reported with Rituxan. Treatment with these agents should be stopped while you have an active infection and are taking an antibiotic or if you have a high fever.

Cancer and Lymphoma: People with RA, especially those with more severe disease, have twice the risk of lymphoma compared to people who don't have RA, regardless of treatment. Some studies, but not all, have shown a higher risk of lymphoma, minor skin cancers, and other cancers in patients with RA receiving TNF inhibitors. The number of cancers is low and the FDA is following the data carefully. Currently, TNF inhibitor treatment is not recommended for patients who have lymphoma or have been treated for lymphoma in the past.

Neurologic Eventsc: There are rare neurologic complications from the anti-TNF medications and people with multiple sclerosis should not use them.

Congestive Heart Failure: People with significant congestive heart failure should not take the anti-TNF agents because they have been found to worsen heart failure.
Use of two or more biologic agents at the same time is not recommended.

Points to remember:
Biologic agents represent a new kind of treatment for patients with inflammatory arthritis, like RA. They are expensive (usually over $15,000 per year in the US), effective and well tolerated in most patients, but do increase the risk of infections and may increase the risk of certain types of cancers. Their safety can be enhanced by proper screening procedures (e.g., TB skin test) and periodic monitoring of blood tests by your doctor. Patients should request and read educational materials (including videos) from the doctor who prescribes these medicines.

Uncontrolled or poorly controlled RA increases the risk of strokes and heart attacks and leads to declines in activity, joint replacement, and early death - especially for people with very active arthritis. Treatment with biologic agents can protect joints from damage and preserve mobility and independence. Weighing the risks and benefits of these new treatments is best done by patients and their physicians who can assess their particular risk factors.

For more information
Your physician may have patient education material on biologic drugs. This information may come in the form of either pamphlets or videos written by either the Arthritis Foundation or the manufacturers of that product.