Anti-TNF Therapy and Cancer Risk in Patients with Autoimmune Disorders

Karen B Onel¹ and Kenan Onel¹,²

¹Department of Pediatrics and ²Committee on Cancer Biology, University of Chicago, Chicago, IL 60637

Correspondence: Inquiries should be directed to
Kenan Onel, M.D., Ph.D.
Section of Hematology/Oncology
Department of Pediatrics
University of Chicago
900 East 57th Street, Rm 5140
MC 4060
Chicago, IL 60637
Phone 773-702-4919
Fax 773-834-1329
konel@uchicago.edu

Abstract: 121 words
Word count: 3105 words
Abstract

TNF inhibitors are extremely effective therapies for a wide range of rheumatologic and other inflammatory conditions. Over the last decade, they have been used to treat millions of individuals worldwide with good results. Although apparently safe in clinical trials, broad usage had revealed unsuspected toxicities, such as severe infections. Most ominously, numerous reports have suggested that patients treated with these agents are at increased risk for malignancies, in particular, hematological malignancies. The purpose of this review is to assess the evidence that both TNF inhibition and the underlying autoimmune diseases themselves are associated with increased cancer risk, and to consider pathways that may underlie these risks in order to help patients and clinicians make informed decisions prior to treatment.
Introduction

In the more than 10 years since targeted therapies to inhibit Tumor Necrosis Factor (commercially marketed as Enbrel, Humira, Remicade, Cimzia and Simponi) have been introduced, these medications have proven to be extremely effective treatments for a wide variety of rheumatologic conditions including both childhood and adult arthritis, psoriasis, uveitis, and many different vasculitides. They have changed the outlook for the better for millions world-wide.

Despite the beneficial effect of these medications, their use is not without risk. Although adverse events were limited in the initial clinical trials, broader usage has led to the identification of numerous relatively common side effects. TNF is an important pro-inflammatory cytokine, and as such, may be required to provide protection from infectious organisms. Soon after TNF inhibitors were licensed for use, an increased risk of morbidity and mortality from infections was seen(1, 2). Although rheumatoid arthritis (RA) patients with severe disease have a known significant increase in infection related deaths, the risk appeared to increase two-fold while being treated with TNF inhibitors(2). In addition, reactivation of tuberculosis (TB) and fungal infections was noted to be a particular risk; for that reason, patients are screened for TB before embarking upon the use of TNF blocking agents and then annually thereafter(3, 4).

The first reports of an association between the use of TNF inhibitors and cancer occurred shortly after these medications became widely available(5-7). Understanding the basis for the increased risk of cancer in patients treated by TNF inhibition has proven difficult. Many rheumatologic diseases are themselves associated with an increased risk of malignancy, as are many of the other medications with which patients are routinely treated(8-11). Because there is great heterogeneity in both autoimmune disease types and in treatment protocols, clear answers have not been forthcoming.
To understand why treatment with anti-TNF agents might be associated with an increased risk of malignancy in patients with autoimmune diseases, Demirkaya et al(12) recently assessed the sensitivity of cells from children with juvenile idiopathic arthritis (JIA) receiving anti-TNF therapies to DNA damage induced by reactive oxygen species (ROS) using the comet assay, a microgel electrophoresis technique to assess genotoxic damage at the level of a single cell(13). They found that lymphocytes from children with JIA on anti-TNF therapy were more sensitive to ROS-induced genotoxic stress and were also less efficient at DNA repair than were cells from the same patients prior to the initiation of anti-TNF therapy(12). Thus, this study identifies a pathway by which anti-TNF therapy can modify cancer risk in patients with autoimmune disease and suggests an assay by which patients at high risk can be identified.

**Anti-TNF therapy and cancer**

As early as 1999, a report linked the use of Infliximab to lymphoma in patients with Crohn’s disease (CD)(5). Reports of cancer associated with etanercept and adalimumab followed shortly(6, 7). A systematic review undertaken by investigators from the Mayo Clinic in 2006 found that CD patients treated with TNF inhibitors had more than triple the risk of developing several types of cancer, including lymphomas, skin cancers, gastrointestinal cancers, breast cancer and tumors of the lung than did CD patients treated with placebo or methotrexate(14). The authors found that 29 out of 3493 patients treated with anti-TNF agents developed cancers, as compared to only 3 out of 1428 patients treated with standard therapy. Of note, the risk of cancer was greatest over the first 6-12 months of anti-TNF therapy.

After the initial case reports appeared in the literature, the FDA began an investigation of cancer in adults treated with TNF inhibitors and mandated the reporting of all patients receiving biologic therapy for rheumatic diseases in whom any cancer was
diagnosed. In 2008, the FDA extended its investigation to include cancer risk in children and young adults after it was reported that 10 cases of a rare gastrointestinal lymphoma occurred in pediatric patients with CD treated with anti-TNF agents (15, 16).

All told, the FDA identified 48 children and young adults who developed cancer between 2001 and 2008 while being treated with anti-TNF therapy out of a total of 26,673 treated, for an age-adjusted incidence rate of 25.7 per 100,000 (17) as compared to the reported rate of 16.6 per 100,000 for all US children (17, 18). Importantly, the rate for children with inflammatory disease not treated with anti-TNF agents is unknown. The cancers found in these children included not only gastrointestinal lymphomas, but a wide range of other cancers as well, including leukemia, malignant melanoma and thyroid cancer.

Although many patients had been treated with other cytotoxic agents, such as 6-MP and methotrexate, many had not. Additionally, although cancer was most commonly associated with the use of anti-TNF agents in patients with CD, an increased risk for cancer was also found in children treated with TNF inhibition for other primary autoimmune disorders including JIA. This observation suggested that it was the exposure to anti-TNF drugs that was driving the association, rather than the underlying disease pathology itself. As a result, in August, 2009, the FDA mandated that a specific black box warning be added to the labels of these medications specifically mentioning the association between cancer and the use of these medications in childhood (19).

Potentially confounding the interpretation of these observations, however, was the fact that little clinical information was recorded for these patients; for example, patients were noted to have JIA but no information on disease course was recorded. Additionally, patient years of anti-TNF exposure varied tremendously among patients as did concomitant and antecedent therapies. Consequently, any assessment of the association between cancer susceptibility and anti-TNF therapy was obscured by limited information on both the underlying disease activity and the inflammatory milieu.
Furthermore, no information was obtained with regard to family history or ethnicity. Not all patients were from the United States, and no correction was made for differences in cancer risk among ethnicities or different geographic locations.

Many countries have since set up registries to monitor prospectively adverse effects for all patients taking TNF inhibitors. There is, however, tremendous heterogeneity in data derived from these registries. Results from the French registry after 3 years of follow-up noted 38 cases of lymphoma for 57,711 patients years of anti-TNF treatment, of which 31 were non-Hodgkin's lymphoma (NHL) (26 B cell and five T cell), five were Hodgkin's lymphoma (HL), and two were Hodgkin's-like lymphomas yielding an SIR for lymphoma of 2.4(20). The Danish and Swedish experiences, however, were completely different. The Danes found a SIR for cancer development of less than 1 for patients treated with infliximab, and the Swedes also found no elevation of cancer risk with use of any of the three TNF blockers irrespective of follow-up time(21, 22).

Why might the results of these studies differ so dramatically? Certainly, population differences, differences in the distribution of autoimmune diseases among the different populations, or differences in study design all contribute. Nonetheless, there is a tremendous difference between a SIR of 2.4 and a SIR of less than 1. The implications of these results for doctors and patients are very significant, underscoring the need for additional consideration and further large-scale studies.

Perhaps most importantly, there are considerable data to indicate that different inflammatory disorders are themselves differently associated with cancer risk. Thus, comparing data from registries comprised of patients with different proportions of primary diagnoses may significantly bias any analysis of the effect of anti-TNF therapy on cancer risk. Specifically with regard to patients with RA, for example, a recent comparison of the Swedish Early RA Registry and the Swedish Cancer Registry found a SIR for all
types of lymphoma of 1.75 regardless of medications used(9). A similar Scottish study found that among RA patients, there was an increased risk for hematopoietic (SIR = 1.76), lung (SIR = 1.44) and prostate (SIR = 1.26) cancers. Reduced risk was seen for colorectal cancer (SIR = 0.71), and, among females for stomach cancer (SIR = 0.70)(23). This excess risk for hematopoietic cancer and reduced risk for colorectal and stomach cancers were sustained over 10 years of follow-up(24, 25). In contrast, a Canadian study reported no increased risk for lymphoma, but an increased risk for leukemia was observed, as was, once again, a reduced risk for colorectal cancer among patients with RA (26). Additionally, many patients with JIA and RA often have a second autoimmune disease such as Hashimoto’s thyroiditis(27) or Celiac disease(28) that are also associated with an increased risk of cancer. The reported range of relative risk for cancer in Hashimoto’s thyroiditis is 3-4 and for patients with Celiac Disease, it is 3-6. The modifying effect of anti-TNF agents on cancer susceptibility in patients with more than one cancer-predisposing condition is unknown(29).

Another critical variable to be considered is the choice of medication itself. Although TNF inhibitors are generally thought of as a common class of drugs, biologically they are quite distinct. Enbrel (etanercept) is a fusion protein that is able to bind to TNF. Remicade (infliximab), Humira (adalimumab), Simponi (golimumab) and Cimzia (certilizumab pegol) are all neutralizing monoclonal antibodies directed against TNF. Some studies have suggested that the risk of malignancy is lower for patients with RA treated with etanercept than with the other medications. A recent meta-analysis of 9 trials including 3316 patients, 2244 of whom received etanercept, did not show a statistically significant increase in cancer development in those receiving etanercept(30). Close analysis of the French registry subjects also revealed that while patients receiving adalimumab or infliximab had a SIR of 4.1 and 3.6, respectively, for cancer development, the SIR for patients receiving etanercept or methotrexate was only
This difference may relate to the shorter half-life of etanercept (4 days versus 7.7-9.5 days for infliximab and 14 days for adalimumab, certilizumab pegol and golimumab) or to the structure of the medications themselves. As newer agents become available with different structures or longer half-lives, the relative contribution of each to risk will become clearer. In many of the registry studies and in clinical practice, the effects of these potentially important differences are confounded, as patients are frequently treated with multiple different drugs over the course of their disease.

The impact of non-biologic anti-rheumatic drugs must also be taken into consideration. Certainly, numerous other medications used to treat RA, including azathioprine and cyclophosphamide, are known to be tumorigenic. A meta-analysis of 21 studies from 1990 to 2007 looking at patients with RA treated with both non-biologic and biologic disease modifying agents showed a relative risk of over 2 for lymphoma regardless of medications (HL>NHL), and a reduced risk for both breast and colon cancer(31).

**Anti-TNF therapy and mechanisms of carcinogenesis in autoimmune disorders**

Because clinical studies have yielded conflicting results implicating both disease and treatments, an understanding of the mechanism whereby disease and therapy can lead to carcinogenesis is crucial. Family studies can help to separate disease from drug effects. A Swedish study of patients with RA and their first-degree relatives without RA did not show an increased risk of lymphoma in family members while demonstrating an increased risk for lymphoma in the patients themselves(32). A Scandinavian case-control study revealed an increased risk of Hodgkin’s lymphoma associated with a family history of sarcoidosis and ulcerative colitis(10). A third family study also found that a family history of systemic autoimmune disease (autoimmune hemolytic anemia, Hashimoto thyroiditis, CD, psoriasis, and sarcoidosis) was modestly associated with...
Non-Hodgkin’s lymphoma, although this association was not statistically significant (33). These studies suggest that there are disease-specific predispositions to cancer in families with autoimmune diseases, although the effect size is small.

Another way to separate the effects of drug from that of disease is to consider cancer development in a wide array of rheumatologic diseases where multiple different therapies are used. An association between SLE and cancer has been unambiguously confirmed in several large international multi-center studies (34-38). Strikingly, as for RA, the cancer risk in SLE is most significant for hematological malignancies (SIR 2.75, 95% CI 2.13-3.49) (34).

This association is not surprising, as hematological malignancies and autoimmune diseases are likely to share a similar underlying inflammatory etiology (29). Ectopic germinal center formation like that seen in the rheumatoid synovium provides a location for chronic immune stimulation and lymphomatogenesis where sustained B cell proliferation may lead the emergence of cancerous clones (29, 39).

Altered cytokine profiles that are common to both disease types may also be responsible for the shared risk phenotype. IL-10 and TNF, both of which are high in autoimmune diseases, may also act as growth factors for B-cell lymphomas (40). The balance of cytokines may be important. Polymorphisms in TNF, IL-4 and IL-10 have all been associated both with autoimmune diseases and an increased risk of lymphomas (41, 42). Thus, by inhibiting TNF, the balance may be shifted from autoimmunity to cancer.

Other studies of shared genetic susceptibilities to malignancy and autoimmune disease have implicated apoptotic pathways (43). As the central mediator of apoptosis in response to a variety of stresses, the p53 tumor suppressor is the critical barrier against malignant transformation; as such, it is likely to be an important determinant of the balance between autoimmunity and cancer. Several groups have investigated the function of the p53 and DNA damage response pathways in patients with arthritis to
determine whether alterations in these pathways could lead to inflammation, oncogenesis or both. Abou-Shousha et al found that levels of p53 were significantly higher in the supernatant from cultured peripheral blood mononuclear cells (PBMCs) derived from patients with RA as compared to those with OA. In addition, there was a significant positive correlation between p53 levels and the disease activity score. Independent studies from 3 groups have indicated that p53 mutations can and do occur in RA synovial tissue samples derived from a subset of RA patients. Inactivation of p53 may contribute to the invasiveness of fibroblasts and to the high-level expression of cartilage degradation enzymes as well(44).

Not surprisingly, p53 mutations have implications for the development of lymphoproliferative disease in rheumatoid arthritis. Xu et al found that the frequency of p53 mutations in RA patients who had not been treated with methotrexate and developed lymphoproliferative disease was significantly higher than those who had been treated with methotrexate. Patients with lymphoproliferative disease with p53 gene mutations had more advanced diseases and an unfavorable prognosis as compared to those without mutations. Hoshida et al found similar results(45).

p53 is not the only important protein linked to abnormalities in the balance between DNA damage and repair. Shao et al found that in naive CD4 CD45RA(+) T cells from RA patients, DNA damage load and apoptosis rates were markedly higher than in healthy controls; repair of radiation-induced DNA breaks was blunted and delayed(46). DNA damage was highest in newly diagnosed untreated patients, and T cells from RA patients did not produce as much mRNA and protein of the DNA signaling kinase, ataxia telangiectasia mutated (ATM), as compared to healthy controls.

The results of genome-wide studies suggest that the use of anti-TNF therapies in autoimmune diseases may further alter the function of apoptotic and repair pathways in patients with autoimmune disorders, thereby influencing the risk of malignancy in this
already susceptible population. Junta et al used gene expression profiling of PBMCs from RA patients to identify specific genes associated with disease and/or therapies (disease modifying anti-rheumatic drugs, and anti-TNF agents)(47). Ninety-one genes were associated with disease activity. They were largely in pathways involved in signal transduction, apoptosis, response to stress and DNA damage. These genes could be important for further study to investigate the relationship among DNA damage, DNA repair, and oncogenesis in patients with autoimmune diseases. Twenty-eight genes involved in intracellular signaling cascades, protein phosphorylation, and protein transport were associated with TNF receptor blockade. Differences in these pathways may point to patients at particular risk for malignancy when treated with these agents.

Defective DNA repair is a well-characterized mechanism by which somatic mutations can accumulate. Using the comet assay, one group found that patients with RA exhibited increased DNA damage as compared to normal healthy controls, and that damage correlated with disease activity(48). Although they included patients that had never been treated, they did not comment on the relationship between specific medications and level of DNA damage. As already described, another group demonstrated that this proclivity to accumulate DNA damage in patients with autoimmune disease is exacerbated by exposure to anti-TNF agents(12).

Thus, both genetically and functionally, considerable data indicate that patients with autoimmune diseases are inherently more sensitive to DNA damage, and inherently less able to deal with its consequences, than are healthy controls. Furthermore, the use of anti-TNF agents can potentiate this effect. Taken together, these observations suggest that some patients with autoimmune disease may be predisposed to cancer because of elevated levels of mutation acquisition resulting from both their underlying disease and the use of anti-TNF therapy.
Conclusions

Clearly, there are multiple genetic pathways that regulate the DNA damage response. Although RA and JIA patients may differ as a group from healthy controls, there are many possible etiologies for these differences, making cancer risk assessment for any individual patient challenging. Autoimmune diseases are themselves likely to be associated with an increased risk for malignancy. Additionally, for any specific child or adult with a severely disabling or even fatal inflammatory disorder, the significance of a three-fold increase in risk of a rare event such as malignancy is low, and should not preclude treatment with anti-TNF agents. Even among those individuals treated with these drugs who have cancer-associated genetic variants, there will be many more individuals who do not develop a malignancy than there will be individuals who do. Furthermore, complex diseases such as cancer result from the actions and interactions of multiple genetic factors, as well as a variety of difficult to quantify non-genetic factors and oncogenic exposures. Currently, there is no satisfactory way to assess how these gene-by-gene or gene-by-environment interactions might alter the contribution of any pathway to disease risk. Thus, clinicians are faced with a dilemma – to treat or not to treat, and if they choose to treat, with what and for how long? The comet assay may help identify patients with an increased DNA damage burden, or an impaired capacity for DNA repair who may be at increased risk for cancer, and thus, may help guide therapeutic decision making on an individualized basis.

Recognizing the tremendous clinical benefit of TNF blockade, but cognizant of the risk of toxicities associated with these agents, it is clear that considerable work remains before the genetic and functional underpinnings of differential susceptibilities to biologic agents can be fully explained. Despite the difficulties, the need for these studies is great, in order to identify the patients most likely to benefit from anti-TNF therapy, as well as the patients most at risk for their toxic and sometimes lethal side effects.
References


17. Questions and Answers - TNF Blockers
19. FDA: Cancer Warnings Required for TNF Blockers.