

TNF- α inhibitors: are they carcinogenic?

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Abstract: Biologic therapy has increasingly been used in the treatment of chronic diseases. Tumor necrosis factor (TNF) is a cytokine implicated in the pathogenesis of rheumatoid arthritis and inflammatory bowel disease. Anti-TNF therapy is being used in the treatment of these conditions. Since the introduction of anti-TNF agents, there have been many case reports of development of malignancy after the initiation of anti-TNF therapy. With increasing case reports, there is growing concern that anti-TNF therapy, albeit useful in the treatment of these chronic conditions, might be associated with the development of malignancy in patients. In this review we examine the different anti-TNF agents and different studies to evaluate any possible association between use of any anti-TNF agent and development of malignancy.

Keywords: tumor necrosis factor inhibitor, malignancy, rheumatoid arthritis, inflammatory bowel disease

Introduction

Cytokines are proteins secreted by different types of cells, which in turn act on the cells which secrete them (autocrine action) or on surrounding cells (paracrine action) or which act systemically away from the local source of secretion (endocrine action). A wide array of cytokines is known. Cytokines are critical for many physiologic processes including hematopoiesis, immune responses, and inflammation.

Tumor necrosis factor (TNF)- α and - β are both cytokines with pleotropic activity. Both play crucial roles in inflammation, are pro-inflammatory, and act on different aspects of inflammation like chemotaxis and cytokine production. They are also involved in immune regulation. Many different TNF ligands and their respective receptors have been identified.

Due to its pivotal role in inflammation and immune response, TNF- α and - β are both involved in the pathogenesis of immune diseases such as rheumatoid arthritis (RA), Crohn's disease, asthma, and psoriasis.¹ Table 1 lists the diseases which are associated with TNF. TNF- α inhibitors have been tried in clinical practice to control those diseases and malignancies associated with TNF use in these diseases.

Chronic inflammation is related to carcinogenesis. Chronic inflammation leads to chronic cellular proliferation and subsequently has been linked to carcinoma development. For example, patients with chronic ulcers are at a risk of development of squamous cell carcinoma of the skin. Higher levels of adenocarcinoma of the colon have been documented in patients with Crohn's disease, and RA is also associated with an increased incidence of many cancers such as lymphoma and lung cancer.²

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Table 1 Diseases in which tumor necrosis factor- α (TNF- α) is implicated, and clinical uses of TNF- α inhibitors

| Diseases in which TNF- α is implicated in the pathophysiology | TNF- α inhibitors use in clinical practice | Reported malignancies associated with anti-TNF agent use in these conditions |
|--|--|--|
| Rheumatoid arthritis | Etanercept, adalimumab | Lymphoma, leukemia, solid organ malignancies, nonmelanoma skin cancer |
| Psoriasis | Infliximab, etanercept | Lymphoma, leukemia, nonmelanoma skin cancer, melanoma |
| Crohn's disease | Infliximab in severe disease refractory to other interventions | Lymphoma, leukemia, solid organ malignancies |
| Ankylosing spondylitis | Etanercept, infliximab | – |
| Asthma | No TNF- α inhibitors in clinical use | – |

A healthy immune system is required for the maintenance of the genome and prevention of cancer development. A healthy immune system is also responsible for detection and removal of cancer cells, a process known as immune surveillance. Cancer cells which escape destruction by the immune system are specific for expressing antigens not recognized by the immune system, or for expressing antigens which are not detected by the immune system as foreign. Cancer cells also have an immunosuppressive effect, thus decreasing the ability of the immune system to eliminate cancer. The immune system thus contributes to the final phenotypic characteristics of tumor, a process known as immune editing.³

With this profound role that immunity plays in the prevention and final phenotypic characteristic of cancer, immune dysfunction helps contribute to the development of cancer. With TNF- α playing a pivotal role in immune function and inflammation, it has also been associated with carcinogenesis. RA, psoriasis, and Crohn's disease are all diseases in which there is immune dysfunction to some degree and in which there is a higher risk of carcinogenesis compared with the general population. TNF- α is intricately involved in immunomodulation. TNF family receptor CD30 is found on activated B and T lymphocytes, while CD40, another TNF family receptor, is found on normal B lymphocytes, monocytes, and dendritic cells. These receptors and their ligands play a role in every stage of the immune response, including priming of antigen presenting cells, cytokine release in response to antigens, stimulation and activation of helper and cytotoxic T cells, antibody production, and class switching of antibodies by B cells. In addition, CD30 receptor and CD40 ligand are expressed in a number of B and T cell lymphomas and leukemias, and high levels of soluble CD30 receptor correlate with poor prognosis in patients with anaplastic large-cell lymphoma and Hodgkin's disease.⁴

Pathophysiology of TNF- α

TNF- α is thus linked to immune response, inflammation, and carcinogenesis, although in some studies it has been shown to be associated with antitumor activity.⁷ TNF- α has been shown to be pathogenic in development of myeloma directly and by induction of interleukin 6, which in turn promotes myeloma bone disease and myeloma cell proliferation. On the other hand, TNF- α has also been shown to be involved in direct cancer cell lysis of leukemia cell lines and it has been shown to potentiate the antineoplastic effect of many chemotherapeutic agents against leukemia and lymphoma cell lines.⁵⁻⁸

TNF- α along with its different ligands, especially TRAIL (TNF-related apoptosis-inducing ligand) and receptors, is involved in induction of apoptosis through interaction with death domain containing proteins, Fas associated death domain, and caspases. It can also result in inflammation and proliferation of cells via nuclear factor- κ B (NF- κ B) and mitogen-activated protein kinase pathways, which are both in turn also associated with carcinogenesis. There are NF- κ B responsive elements in the promotor region of many genes involved in carcinogenesis and cell cycle progression.^{9,10}

The dual nature of TNF- α activity may be responsible for its paradoxical anti- and protumor activities depending on the cell, environment, dose, and other factors. TNF- α inhibitors are presently used in the treatment of RA, Crohn's disease, ankylosing spondylitis, and psoriasis – diseases which are all associated with immune-mediated tissue damage and inflammation, all of which are associated with increased risk of carcinogenesis. In patients with RA, drugs used to alter the course of disease, called disease-modifying drugs, are also associated with carcinogenesis; for example, azathioprine and cyclophosphamide.^{11,12} Unequivocal evidence linking methotrexate treatment in RA to carcinogenesis, however, is lacking.¹³

Clinical experience with TNF- α inhibitors and carcinogenesis

There are five different TNF- α inhibitors in clinical use at this time:

- Etanercept is a dimeric fusion molecule with fusion of human immunoglobulin Fc fraction with TNF- α receptor gene. It acts by binding TNF- α and making less available for biological activity. It has been used clinically in the treatment of RA, psoriasis, psoriatic arthritis, and ankylosing spondylitis.
- Infliximab is a chimeric mouse/human monoclonal antibody against TNF- α clinically used for the treatment of Crohn's disease and ulcerative colitis.
- Adalimumab is a completely human monoclonal antibody against TNF- α used for treatment of RA.
- Certolizumab pegol is the antigen-binding fragment of humanized monoclonal anti-TNF antibody bound to polyethylene glycol for longer action. It is currently used in moderate to severe Crohn's disease.
- Golimumab is a human monoclonal anti-TNF antibody used for the treatment of moderate to severe RA, psoriatic arthritis, and ankylosing spondylitis.

In a trial to evaluate the efficacy of anti-TNF- α agent infliximab in combination with methotrexate in the treatment of RA, it was shown that anti-TNF- α antibodies do provide long-term relief when used in combination with methotrexate, compared with methotrexate alone. There was a significant number of patients who developed positive anti-nuclear antibodies and anti-double strand DNA after treatment with infliximab, indicating that infliximab results in immune modification. Five patients developed malignancy after starting anti-TNF- α therapy within 30 weeks. This included a patient with basal cell carcinoma and another patient with moderately differentiated rectal carcinoma. The number of cases of cancer development was too low to be significantly linked with anti-TNF- α therapy, and was similar to that reported by the SEER database.¹⁴

With TNF- α being so intricately involved in immune response and lymphomas and leukemias, there has been concern for development of hematologic malignancies with use of TNF- α inhibitor therapy.

There is indeed evidence that TNF- α is associated with survival and expansion of multiple myeloma cells *in vitro*. TNF- α was also associated with cutaneous T cell lymphoma development. Etanercept was used in trials in patients with these two diseases without any significant response. In multiple myeloma patients, it actually increased TNF- α

levels, which might have resulted in poor survival.^{15,16} Bupropion, a common antidepressant, was shown to induce remission in a patient with Crohn's disease. The likely mechanism of action was thought to be decreased TNF- α synthesis by bupropion.¹⁷

The risk of development of lymphoma in patients with RA increases with the severity of disease.^{18–20} These findings make it hard to elucidate the link between anti-TNF- α therapy and development of lymphoma, especially since patients with severe RA are treated with anti-TNF- α therapy.

TNF- α and hematologic malignancies

Lymphoma has been reported after TNF- α receptor use. Braun et al reported 26 cases of lymphoma after treatment with etanercept (18 cases) and infliximab (8 cases) in patients being treated for RA and Crohn's disease. These cases were reported to the US Food and Drug Administration as part of the post marketing surveillance. These cases developed on average 8 weeks after initiation of treatment. Two cases of lymphoma (one in the etanercept group and one in the infliximab group) resolved after stopping anti-TNF- α treatment, without the need for any other therapy. The age-adjusted incidence of lymphoma during this time (1992–1998) was 18.3/100,000. As the exact number of patients taking these medications was not known, and due to widespread underreporting of these adverse effects, it was difficult to estimate whether this represented an increase in the rate of lymphoma or not. One of 18 patients who were treated with etanercept developed Hodgkin's lymphoma while three out of eight patients who were treated with infliximab developed heart disease. The lymphomas were predominantly B cell lymphomas (13 out of 18 in etanercept-treated patients and 5 out of 8 in infliximab-treated patients), as would be expected for lymphoma development after immune suppression.²¹ There were two cases of lymphoma in the group which regressed upon stopping of anti-TNF therapy. A similar incidence of development of lymphomatoid papulosis (LP) was reported after use of infliximab along with azathioprine for treatment of Crohn's disease in a 21-year-old male. He developed cutaneous T cell malignancy (LP) 2 years after being on these two antiagents. The cutaneous skin lesions resolved in a few months after stopping anti-TNF therapy.²²

Following this, Wolfe et al reported the standard incidence rates (SIR) of development of lymphoma in 18572 RA patients who they followed prospectively to be 1.9 (1.3–2.7) for lymphoma development in these patients.

SIR of development of lymphoma after use of anti-TNF- α therapy (infliximab or etanercept) was 2.9 (1.7–4.9). SIR of development of lymphoma after methotrexate use was 1.7 (0.9–3.2), indicating that methotrexate use was not associated with the development of lymphoma. One of the confounding findings in this study was that patients who had severe RA, and hence were already at an increased risk of lymphoma development, were the ones who received anti-TNF- α therapy. This finding makes it difficult to elucidate whether the disease or treatment or its combination contribute to the increased incidence of lymphoma in this group. This prospective study did not observe the grouping of lymphoma cases in the early time period after the start of treatment as had been observed in other studies.²³

A population-based study undertaken by South Swedish Arthritis Treatment Group (SSATG) was reported by Geborek et al. They compared 757 patients who received anti-TNF- α therapy for RA with an 800-patient population group which did not receive this treatment. They followed these patients for 5 years from 1997 to 2002 and did not note any increase in overall malignancies in the anti-TNF- α group compared with the control group. There was an indication of an increase in relative risk of lymphoma development in the treatment group, but the number of lymphoma cases was too small (five in the treatment group, compared with two in the control group) to draw any conclusion. The relative risk of lymphoma development in patients who received anti-TNF- α therapy was 4.9 (0.9–26.2). It is important to note that patients with previous cancers were excluded from receiving anti-TNF- α treatment. Also the types of lymphomas observed in patients treated with anti-TNF- α treatment were predominantly B cell lymphomas, similar to that observed in patients with RA, lending support to the hypothesis that these lymphomas were related to the underlying arthritis rather than its treatment.^{24,25} Following this, a meta analysis of 18 studies including 8808 RA patients by Leombruno did not find an increased incidence of lymphoma or any nonhematologic cancer in patients treated with anti-TNF therapy. They evaluated studies which included treatment with etanercept, infliximab, and adalimumab. The information about malignancy was not uniformly described in the studies analyzed, and there was concern over under and over reporting of malignancies in some included studies. The median follow up of the patients was less than 1 year, so the meta analysis could not speculate about malignancies which developed after 1 year of follow up.²⁶ We reported the development of acute myeloid leukemia (AML) in a 57-year-old patient who received etanercept therapy for psoriatic arthritis for 6 months. Bone marrow biopsy prior to

the development of leukemia were not available to confirm or exclude myelodysplastic syndrome prior to initiation of anti-TNF- α therapy. The patient developed myelodysplastic syndrome with acute myeloid leukemia (MDS/AML) which was resistant to standard treatments and succumbed to the disease. With this and other such case reports of leukemia development in patients after anti-TNF- α therapy, we recommend routine blood counts and consideration of bone marrow biopsy of patients with abnormal blood counts prior to initiation of anti-TNF- α therapy to exclude myelodysplasia as a predisposing factor to malignancy.^{27–29}

Anti-TNF- α therapy and solid tumors

Etanercept use has been associated with the development of solid organ malignancies in patients treated for Wegener's granulomatosis. In one study, 6 of 89 patients randomized to etanercept treatment in addition to standard therapy for Wegener's granulomatosis (ie, cyclophosphamide) developed solid organ malignancies during a median follow up of 27 months, compared with no patients who received cyclophosphamide alone ($P = 0.01$). There were two cases of colon adenocarcinoma and single cases of cholangiocarcinoma, renal cell carcinoma, breast cancer, and liposarcoma.³⁰

Infliximab use in patients with inflammatory bowel disease has been associated with development of carcinoid tumor, signet ring cell carcinoma of the bowel, breast cancer, lung cancer, and colorectal cancer.³¹

It was further shown in another study that 5 of 428 patients who received infliximab therapy for methotrexate refractory RA developed malignancy within 30 weeks of initiation of treatment. The incidence of malignancy in this group was similar to that expected of a similar population not treated with anti-TNF- α therapy per the SEER database. In another study evaluating treatment with infliximab along with methotrexate in patients with early RA, 4 of 325 patients developed cancer. These included a case of endometrial carcinoma, pancreatic carcinoma, colonic adenocarcinoma, and a case of AML. This was not higher than the expected rate reported by the SEER database.^{14,32}

Adalimumab a fully humanized monoclonal antibody against TNF- α and has been used for RA treatment recently. Adalimumab treatment in patients refractory to other forms of treatment or adalimumab treatment concomitant with other antirheumatoid treatment like methotrexate has not been shown to increase the rate of lymphomatous or nonlymphomatous malignancy over and above that expected

in the general population.^{33,34} However, a recent meta analysis of nine trials of anti-TNF- α therapy in RA patients reported an increased odds ratio (OR) of development of malignancy in patients treated with infliximab or adalimumab, especially those treated with higher doses. OR for malignancy development was 3.3 (1.2–9.1).³⁵ Though the meta analysis showed an increased OR of development of malignancy in patients treated with anti-TNF- α therapy, the studies included in the analysis had varying duration of follow up and varying doses of anti-TNF- α agents. A subsequent large observation study done, however, suggested that there was no increase in overall malignancies in patients treated with anti-TNF- α therapy compared with those not treated with the same in RA patients.³⁶ Biancone et al evaluated the development of new cancers in 404 patients with Crohn's disease who were treated with infliximab and compared them to a group of 404 patients with Crohn's disease who did not receive infliximab for a period of 5 years and did not find an increase in the incidence of malignancy in the group treated with infliximab.³⁷ A similar result was obtained by Lichtenstein et al in evaluating infliximab therapy for CD patients. They followed 6273 patients with CD for 15000 patient years in the TREAT registry and did not find an increase in the incidence of malignancy in the infliximab-treated group.³⁸

Lees et al evaluated the safety of anti-TNF therapy in patients with Crohn's disease and ulcerative colitis. They evaluated 202 patients with median follow up of 2.4 years. They noted three cases of hematological malignancy and three cases of bronchogenic carcinoma.³⁹

There have been recent studies suggestive of increased incidence of lung cancer in elderly smokers and patients with chronic obstructive pulmonary disease (COPD).^{40,41} Two elderly smokers developed infliximab-related lung cancer in a Mayo clinic trial of 500 patients with Crohn's disease.⁴⁰ Of the 157 patients in the infliximab group, in patients with COPD, there were nine cases of malignancy development compared with 1 of 77 patients in the control group. Of the nine cases of malignancy in the treatment group, four were lung cancers.⁴¹

There has been a case report of non small cell lung cancer development in a patient who received infliximab and later adalimumab. The tumor was positive for TNF 1 and 2 receptors. It regressed and stayed in remission after discontinuing anti-TNF therapy.⁴²

Certolizumab Pegol has shown efficacy in patients with Crohn's disease who are infliximab-naïve and also in those who have been treated with infliximab before.⁴³ In a placebo-controlled double-blind trial of 662 patients with

Crohn's disease, certolizumab did not increase the incidence of malignancy compared with placebo.⁴⁴

Golimumab, a human monoclonal anti-TNF antibody, has shown efficacy in patients with RA who had previously been treated with other anti-TNF agents. A systemic review of a study including 1231 patients who were treated with golimumab and 483 control patients did not find any difference in the rates of malignancy in both groups.⁴⁵ Another study noted a nonsignificant increase in the rates of overall malignancy and basal cell carcinoma in patients treated with golimumab in combination with disease-modifying antirheumatic drugs (DMARD) (891 patients) when compared with placebo alone (666 patients). Though the results of this meta analysis are not statistically significant, the trend towards increased malignancy and basal cell carcinoma should be kept in mind when using golimumab in combination with DMARDs.⁴⁶

Anti-TNF- α therapy and skin cancer

Anti-TNF- α therapy has been associated with melanoma and nonmelanotic skin cancers (SCC and BCC) though no study to date has conclusively proved the increased incidence of either of these with use of anti-TNF- α therapy in patients. There have been incidences of development of acute keratoacanthomas and SCC in patients who are treated with anti-TNF- α therapy. The short time of development of these SCC and keratoacanthoma again point toward the de-repression of latent malignancy as the potential mechanism of neoplasm potentiation.^{47,48}

Lebwohl et al studied 1442 patients who received etanercept for RA and followed them for 5 years and did not find an increased incidence of squamous cell carcinoma in these patients (4 cases over 5 years) compared to the general population (13.9 cases in Arizona and 5.9 in Minnesota). This and another study by Burge did not support the association of anti-TNF- α therapy with nonmelanotic skin cancer.^{49,50}

A multivariate Cox proportional hazard analysis of rheumatoid and osteoarthritis patients indicated that prednisone use and concomitant use of anti-TNF- α therapy and methotrexate were significantly associated with the development of nonmelanotic skin cancers, ie, SCC and BCC. Multiple fields of data are missing from the study, including confirmed diagnosis of patients as having osteoarthritis or RA, lack of family history, and past history of skin cancers. The duration and doses of anti-TNF- α agents used were also not available. These restrictions and the observational nature, does not support the strong association of anti-TNF- α

therapy with skin cancer.⁵¹ A recent large observational study of 13,001 patients, however, did report an increased OR of development of nonmelanotic skin cancer in patients who received anti-TNF- α therapy (OR of 1.5 with 95% confidence interval 1.2–1.8; P value < 0.001), but did not report any increase in the OR of development of any other malignancy.³⁶

Contraindications to use of anti-TNF agents

Other instances of development of carcinomas within a short time of anti-TNF- α therapy indicate a potential derepression of occult malignancy as a potential method of development of carcinoma. An occult malignancy which was hitherto in check by the immune system, developed into a full blown cancer by the immune modification brought about by anti-TNF- α therapy. With this in mind, the British Society of Rheumatology recommends exercising caution while prescribing anti-TNF- α drugs to patients with prior malignancy or premalignant conditions like Barrett's esophagus, cervical dysplasia, and large bowel polyps. Myelodysplastic syndrome should be added to this list as it is a premalignant condition more common in the elderly, increasing in incidence, and associated with leukemia. However, these inhibitors may be used more safely if the patient has not had any recurrence of cancer for 10 years.⁵² The American College of Rheumatology contraindicates the use of anti-TNF agents in patients who had a lymphoid malignancy in the last 5 years.⁵³

Conclusion

Anti-TNF- α inhibitors are potent drugs and have theoretical and real risks in terms of decreasing tumor surveillance and allowing cancer cells to grow and proliferate. Clinical trials have shown that there is a higher than expected rate of lymphoid malignancies after TNF- α , but probably not higher than expected for solid tumors. Whether the higher than expected cancer rates are solely due to drugs or to underlying conditions or genetic predispositions giving rise to the underlying disease and the subsequent cancer is not known. More studies may help to elucidate the link between TNF- α inhibitors and cancer risk. In the meantime, caution should be used in treating patients with active or prior cancer, or those with high risk for developing cancer.

Disclosure

The authors report no conflicts of interest in this work.

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