Is Anti-TNF Therapy Always Prohibited in Patients with Inflammatory Bowel Disease and Previous Malignancy?

by Mark Lust, Simon Travis

INTRODUCTION

The name tumor necrosis factor (TNF) implies, logically enough, an action to necrose tumor cells. Treatment to inhibit TNF (anti-TNF therapy with adalimumab, certolizumab pegol, or infliximab), therefore raises all sorts of alarm bells if a patient has a previous history of malignancy. It implies that it simply shouldn’t be given and, of course, such patients (with the exception of those with a curative resection of basal cell carcinoma) have been excluded from the clinical trials. Is this a no-brainer, or is there wiggle room? It is after all, a problem that we all occasionally face in clinical practice.

By way of example, consider the following case we saw in Oxford recently. A 33-year-old medical colleague was successfully treated for a large cell anaplastic non-Hodgkin’s lymphoma at the age of 16. He was diagnosed with Crohn’s disease (CD) in 2007 and had an ileocolic resection in 2008. He has now (2009) presented with recurrent colonic disease and is steroid-dependent. He clearly requires escalation of medical therapy, but is anti-TNF therapy safe in the context of his previous lymphoma?

Some studies have highlighted the potential for an increased risk of malignancy in patients receiving anti-TNF therapy (1–3), but no study has specifically asked whether TNF blockade increases the risk of recurrent cancer in patients with previous malignancy. Consequently it is unclear whether treatment with anti-TNF agents should be avoided in these patients. This review will ask how TNF blockade might promote tumor recurrence or progression, summarize associations between anti-TNF therapy and malignancy, and offer practical advice when considering these therapies in patients with previous malignancy.

HOW MIGHT ANTI-TNF THERAPY PROMOTE TUMOR RECURRENCE OR PROGRESSION?

Initially recognized for its ability to lyse tumor cells, TNF is required for natural killer cell and CD8 lymphocyte-mediated tumor cell death (4). Anti-TNF therapy may therefore increase the risk of development or progression of malignancy. A biological explanation for this risk has been explored in a murine model of chemically-induced metastatic cancer (5). In this model, mouse survival depended on intact adaptive immunity, while experimental depletion of CD4 or CD8 T cells, or neutralization of interferon-gamma in vivo, resulted in tumor progression and death. These mechanisms are TNF-dependent and appear critical to maintaining tumors in a dormant state. On the other hand, signaling via theTNFα-NFκB pathway in intestinal epithelial cells has been shown to be directly involved with colitis-
associated carcinogenesis in another animal model (6). A monoclonal antibody to TNFα actually reduced the rate of neoplasia in this azoxymethane-dextran sodium sulfate murine model. So some theoretical evidence for cancer progression following treatment with anti-TNF therapy exists, but the evidence is inconsistent and what is the real risk of malignancy in patients who have received these agents in practice?

**WHAT IS THE RISK OF MALIGNANCY IN PATIENTS TREATED WITH ANTI-TNF ANTIBODIES?**

There are several reports of cancer developing after anti-TNF therapy (1–3,7,8), but it is difficult to prove a link between exposure and tumor development. This is because patients treated with anti-TNF therapy may already be predisposed to cancer as a consequence of their underlying disease. For example, patients with rheumatoid arthritis (RA) have an increased risk of lymphoma (9,10), while patients with long-standing ulcerative colitis have an increased risk of colon cancer (11). Furthermore, patients with immune-mediated disorders often receive, or have been exposed to other immunomodulators that could independently increase the risk of cancer.

**Malignancy in RCTs of Anti-TNF Therapy for IBD**

Malignancy has been reported in all randomized controlled clinical trials (RCTs) of anti-TNF therapy in IBD, but at a rate no higher than in controls (12–18). A meta-analysis of all six anti-TNF agents (infliximab (IFX), adalimumab, certolizumab, etanercept, oncercept, and CDP571) evaluated in RCTs in 3,955 patients with luminal or fistulizing CD showed no difference in the frequency of malignancy between anti-TNF and control groups (2). Safety data from 10 years’ clinical trial experience with adalimumab in six immune-mediated inflammatory diseases 19, included 19,041 patients of whom 2,228 had CD treated for a total of 2,373 patient-years. The absolute risk of any malignancy was 1.3 per 100 patient-years of treatment, which means that if you were to treat 100 patients for a year, then a malignancy can be expected in every 76 (100/1.3) patients treated. The absolute risk of lymphoma was <0.1 per 100 patient-years of treatment. Put more simply, if you were to treat 1,000 patients for one year (or 100 patients for 10 years), then less than one case of lymphoma can be expected. It is usually easier for patients to understand absolute, rather than relative risks, but the results should be interpreted with caution. RCTs have stringent inclusion and exclusion criteria which may not represent clinical practice. Furthermore, in many of the trials, control subjects were also exposed to at least one dose of anti-TNF therapy and the trials were not powered to detect differences in adverse events. Finally, the duration of follow-up may be too short to detect rare serious events, such as malignancy.

**Malignancy in Real-world IBD Practice**

Post-marketing surveillance provides data from larger numbers of patients, more representative of the population treated and potentially followed over longer periods of time. On the other hand, such data are limited by incomplete or selective reporting and documentation. In an early retrospective cohort of 500 patients with IBD treated with IFX at the Mayo Clinic, nine developed malignant disease, of which three were thought possibly related to IFX (20). In the North American TREAT registry of 6,273 patients followed for a mean of 4.3 years, there was no significant difference in rates of malignancy in patients that did or did not receive IFX (risk ratio = 0.76; 95% confidence interval (95% CI) 0.54–1.07) (21). An Italian multicenter study showed similar prevalence rates of newly diagnosed neoplasia in a group of 404 patients with CD treated with IFX compared to 404 matched CD patients who did not receive IFX (22). A Danish population-based IBD cohort treated with IFX identified 4/651 patients diagnosed with cancer during the study period, compared with 5.9 expected (23). However, the estimate of expected cancer rates was calculated from age- and sex-matched population rates, rather than a matched cohort of IBD patients not treated with IFX. Of note, one of the patients was a 55-year-old woman diagnosed with breast cancer in 2000, who received 4 IFX infusions during 2004 and developed metastatic relapse one year later.

Interpretation of the results is still limited by the relatively short duration of follow-up. Some of the best
data come from a single-center Belgian cohort of 734 patients with IBD treated with a median 6 IFX infusions and followed for a median 58 months, compared to 666 IBD patients that did not receive IFX (24). Fifteen malignancies and eight non-melanoma skin cancers were diagnosed in the IFX-treated group, but this was similar to the malignancy rate in the control group.

Of much greater concern is the potential for the development of hepatosplenic T-cell lymphoma in young male patients with CD treated with anti-TNF therapy and a thiopurine (7). Eighteen cases have been reported to date (Q1 2009). This lymphoma is rare, but aggressive and often fatal. No case has occurred without combination immunosuppression and as yet no case has occurred with methotrexate. Opinion is divided about the best approach, since combining IFX and a thiopurine improves clinical response when treating CD, especially in early disease. Most specialists agree that the remote possibility should at least be discussed with the patient or family, that combining IFX and a thiopurine is done with great caution and that the option of replacing azathioprine or mercaptopurine with methotrexate be considered. The lack of reports related to methotrexate may, however, simply reflect its limited use compared to azathioprine or mercaptopurine.

**Malignancy in RCTs of Anti-TNF Therapy for Other Disease**

In RA, a meta-analysis of nine clinical trials reported a dose-dependent increased risk of malignancy in 3,493 patients treated with IFX or adalimumab compared to 1,512 patients receiving placebo (pooled odds ratio (OR) 3.3; 95% CI 1.2–9.1) (1). None of the trials in this meta-analysis included patients with pre-existing malignancy. In contrast, two large cohort studies failed to demonstrate an increased risk of malignancy associated with the use of anti-TNF therapy in patients with RA (25, 26). Similarly, a longitudinal study of 19,591 patients with RA with 89,710 patient-years of follow-up demonstrated no increased risk of lymphoma in patients that were treated with IFX (3).

While these data are generally reassuring, a placebo-controlled trial of IFX in patients with chronic obstructive pulmonary disease followed for six months reported no less than 10 cancers diagnosed in 157 patients given IFX compared to only one cancer in the placebo group of 77 patients (27). Most cancers involved the respiratory tract and it is possible that anti-TNF therapy accelerated the growth of pre-existing cancers in a smoking population already at high risk. However, the small sample size makes it difficult to draw any firm conclusions. It simply means that the potential for IFX to contribute to the progression of malignancy remains a serious concern.

**WHAT IS THE RISK OF CANCER RECURRENCE OR PROGRESSION AFTER ANTI-TNF THERAPY?**

There are very few data on the risk of anti-TNF therapy in patients with previous malignancy. One abstract reports data from the British Society of Rheumatology Biologics’ Register to assess the potential risk of malignancy associated with starting anti-TNF therapy in patients with RA who had pre-existing cancer (28). Patients who had a malignancy prior to starting anti-TNF therapy had an increased risk of a further malignancy after commencing treatment, compared to those with no previous malignancy. Six of 154 patients (4%) with RA and a previous malignancy developed a new cancer, compared to 158/9,844 patients (1.6%) with RA but no previous malignancy (incidence risk ratio 2.5; 95% CI 1.2–5.8). Of the six cancers that developed in patients with a history of previous malignancy, three occurred in patients who had a malignancy >10 years before starting anti-TNF therapy. Only one was a local recurrence or metastatic spread. These data suggest that patients with RA and pre-existing cancer have a higher risk of developing new malignancy following anti-TNF therapy. On the one hand it means that anti-TNF therapy should be used with great caution in such patients, but on the other hand the risk might still be perceived as low. What is not reassuring is the fact that half occurred a decade after the original cancer.

Other data are anecdotal. Two cases of metastatic colorectal carcinoma are reported after treatment with IFX in patients with previous colonic neoplasia (8). One was in a 70-year-old woman who had had a sigmoid resection for a stage I adenocarcinoma 10 years before being given IFX for the treatment of RA, although she also had a 30-year history of CD, which was inactive. Surveillance colonoscopy one year before the diagnosis
of her second colon cancer was normal with no dysplasia in 32 random colonic biopsies. She received IFX over two years before she developed an obstructing carcinoma in the proximal transverse colon with a liver metastasis. The second case involved a 47-year-old woman with a 20-year history of Crohn’s colitis, controlled by mercaptopurine, who had surveillance colonoscopy every two years. Colonoscopy two years before the diagnosis of colonic carcinoma had shown low grade dysplasia with background inflammation in the ascending and transverse colon. Colonoscopy had been repeated one year later and biopsies from the same areas had shown no evidence of dysplasia. She was started on IFX for symptomatic Crohn’s colitis and received two courses of IFX over two years, although it is not clear how many infusions this involved. Five months after her last infusion, she presented with a palpable abdominal mass due to a poorly differentiated carcinoma of the transverse colon, with a liver metastasis. These two cases are clearly of concern, since both had colonoscopies prior to treatment with IFX and developed metastatic colon cancer within two years.

**SO, SHOULD PATIENTS WITH PREVIOUS MALIGNANCY BE TREATED WITH ANTI-TNF THERAPY?**

Anecdotes and case reports aside, this is an evidence free zone. In general the answer is no, but medicine is always about balancing risks and benefits. There is a theoretical risk that anti-TNF therapy will increase the risk of tumor progression or recurrence in patients with malignant or pre-malignant disease, but controlled data are lacking. The British Society of Rheumatology (BSR) recommends caution before using anti-TNF therapy in patients with previous malignancy or pre-malignant conditions such as Barrett’s esophagus, cervical dysplasia, or colonic polyps (29). With the circumspection of double negatives, the BSR says that there is no established contra-indication to anti-TNF therapy for patients who have been free of recurrence of their malignancy for 10 years. A “cancer-free window” of 10 years is arbitrary and the case report above makes no offer reassurance.

Coming back to our patient, he was commenced on azathioprine after careful discussion. Anti-TNF therapy was not discounted, but will only be considered if azathioprine fails (although methotrexate will be given if he cannot tolerate azathioprine) and after further discussion with him and his specialist oncologist.

The potential benefits of anti-TNF therapy need to be balanced against the potential risks of malignancy or recurrence. Decisions have to be tailored to the individual.

- **In normal circumstances**, the risk of a new malignancy appears so low in patients with active IBD refractory to other therapy, that it is almost always outweighed by the benefits of treatment. Indeed it is difficult to imagine a situation in which the opposite would apply, other than a particularly anxious patient with a strong family history of malignancy.
- For patients with many pre-malignant conditions (including Barrett’s esophagus without dysplasia or colonic polyps), the same must generally apply.
- For established dysplasia, the balance tilts against anti-TNF therapy, although a situation in which a patient has debilitating symptoms from IBD and cervical dysplasia can readily be conceived. In these circumstances anti-TNF therapy in conjunction with treatment of the cervical dysplasia would often be reasonable, but discussion with other specialists (in gynecology, gastroenterology and oncology in this example) would be advisable.
- For patients with a past history of malignancy other than a basal cell carcinoma or curative resection of a squamous cell carcinoma, anti-TNF therapy should generally be avoided, unless there are compelling reasons that it presents the only practical therapeutic option. Specialist advice is again advisable (share the burden of the decision!), including consideration of whether surgery, natalizumab or other therapy is more appropriate for treating the IBD.
- Anti-TNF therapy should almost always be avoided in patients with active malignant disease, because of the risk of accelerating tumor progression and spread.

The principle of primum non nocere (first, do no harm), espoused by William Osler, is sound. The risk, however, of anti-TNF therapy in patients with a previous malignancy or pre-malignant condition is simply not known. Discussion with the patient about all therapeutic options and appropriate specialist advice is necessary before an informed mutual decision can be reached.
References


