

Mounting evidence that anti-tumour necrosis factor- α therapy does not increase the risk of new or recurrent cancer

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Inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory conditions of the intestine affecting 200,000 (1:500) people in the UK, a million people in Europe and 2 million people worldwide (1). They are lifelong conditions with periods of active disease alternating with periods of remission. Usually diagnosed between 10 and 30 years old, IBD causes significant disability, often restricting the ability to work normally. Symptoms vary, but commonly include diarrhoea, abdominal pain, weight loss and blood or mucus in the stool. Patients can also suffer joint, eye and skin problems. The medications used to treat IBD initially aim to reduce inflammation in the gut and induce remission. Once under control, medications are focused on maintaining remission and preventing relapse.

Anti-tumour necrosis factor- α (TNF α) therapies have revolutionised the treatment of IBD and recent evidence supports their use earlier in the disease course (2). Both infliximab, a chimeric monoclonal antibody to TNF α and adalimumab, a recombinant IgG1 human monoclonal antibody that binds to TNF, have been shown to be effective in inducing clinical remission and maintaining response in patients with CD (3-5). They have also been also shown to be effective in the induction and maintenance of UC, although as results from clinical trials have been variable, their role is less accepted (6,7). Despite these medications

being amongst the most thoroughly investigated agents prescribed by gastroenterologists, crucial questions remain regarding their efficacy, when to use them and their risks, including treatment-associated malignancies (8).

The number of cancer diagnoses per year in the UK is 367,000 and increasing (9). With this figure in mind and given an ageing population, it is inevitable that some IBD patients will also develop cancer. Furthermore, immunosuppressive agents used to treat IBD, have been associated with an increased risk of cancer. Studies have shown specifically an increased risk of lymphoma in patients exposed to thiopurines. Less is known about the malignancy-promoting potential of anti-TNF α s, but evidence suggests an increased risk of skin cancer, including melanoma, in patients exposed to a combination of thiopurines and anti-TNF α therapies (10-12). IBD patients with a history of cancer have therefore typically been excluded from anti-TNF α randomised controlled trials because of this theoretical risk of treatment-associated malignancies. This has led to uncertainty in prescribing these medications in this setting (13).

More is known from studies looking at anti-TNF α agents in rheumatoid arthritis (RA). A systematic review by Bongartz *et al.* found that there was a dose-dependent increased risk of malignancy in RA patients treated with anti-TNF α therapy. The number needed to treat to

harm was 154 for 1 additional malignancy during a 6- to 12-month treatment period (14). A further systematic review and meta-analysis by Mariette *et al.* in 2011 showed that RA patients treated with anti-TNF α therapy had an increased risk of skin cancers, although there was no increased risk of lymphoma (15).

There are however, other studies that have disputed these findings. Wolfe and Michaud found no evidence of an increased risk of lymphoma amongst RA patients who received anti-TNF α therapy (16). Furthermore, the population-based study by Silva-Fernández *et al.* concluded that patients with RA and prior malignancy who received an anti-TNF α did not have an increased risk of future malignancy (17).

This conflicting evidence is one of the reasons why there are currently no consensus guidelines on the management of IBD in patients with a previous cancer. The 2010 European Crohn's and Colitis Organisation guidelines indicate that anti-TNF α therapy is contraindicated in patients with a history of lymphoma and "careful consideration should be given to initiating anti-TNF therapy" in those with a history of other cancers (18). The 2009 American College of Gastroenterology and 2010 World Gastroenterology Organisation guidelines do not include any recommendations regarding the management of IBD in patients with a history of cancer (19,20).

Clearly, due to the ethical implications of randomised control trials looking at risk of developing malignancy, more research is needed in this field to overcome the lack of definitive evidence. The nationwide, population-based cohort study by Waljee *et al.* sought to address this ongoing concern (21). The Danish study looked at adults with IBD, RA or psoriasis with a previous diagnosis of cancer. They prospectively recruited patients and followed them up during their anti-TNF α therapy. Participants on anti-TNF α therapy were matched by sex, disease type and cancer type with 10 controls who were not treated with anti-TNF α s. The primary outcome was development of new or recurrent cancer. Overall, 434 patients with immune-mediated disease treated by anti-TNF α therapy and with a previous history of cancer, were matched with 4,328 controls. The incidence of new or recurrent cancer was 30.3 cases (95% CI: 24.0–38.2) per 1,000 person-years in the treatment group and 34.4 cases (95% CI: 31.7–37.3) in the control group. The authors therefore concluded that the use of anti-TNF α therapy was not associated with recurrent or new primary cancer development in patients with previous cancer.

Importantly, subgroup and sensitivity analyses showed that excluding initial diagnosis of non-melanoma skin cancers, examining recurrent and new cancers separately, and taking treatment with other immunosuppressants (such as thiopurines) into account did not affect the primary outcome. Also, timing of anti-TNF α therapy after the initial diagnosis of cancer (<2 or >2 years) did not increase risk of future cancer development. The median follow-up time was 5.6 years after treatment (18,752 person-years), which is longer than other studies, further strengthening the findings' clinical applicability.

Despite this relatively long follow up period, in a clinical context, 5.6 years could be considered a short time. There are other limitations too; although some characteristics were matched in the control group, the age of initial cancer diagnosis was lower in the treatment group. As malignancy is a disease of the ageing, this could mean new cancer diagnoses in the treatment group have been underestimated. It is possible that other, immeasurable confounders also exist between the two groups. Controlling for specific cancer diagnosis, a specific anti-TNF α agent or evaluating the effect of treatment duration was not possible without substantially limiting the statistical power, leaving some key questions unanswered.

The inherent limitations of the study design aside, the unfeasible and unethical nature of a randomised control trial in this setting, means that clinicians will have to rely on large-scale observational data to guide their decision making. This article adds to a growing field of evidence that suggests that there is no increased risk of cancer in patients exposed to anti-TNF α therapy and goes some way to ease the difficult decisions around using these medications in this context.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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