Editorial Commentary

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

Jennifer Phillips

Department of Gastroenterology, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

Correspondence to: Jennifer Phillips. Department of Gastroenterology, University Hospitals Bristol NHS Foundation Trust, Upper Maudlin Street, Bristol BS2 8AE, UK. Email: Jennifer.Phillips3@UHBristol.nhs.uk.

Comment on: Waljee AK, Higgins PDR, Jensen CB, *et al.* Anti-tumour necrosis factor-α therapy and recurrent or new primary cancers in patients with inflammatory bowel disease, rheumatoid arthritis, or psoriasis and previous cancer in Denmark: a nationwide, population-based cohort study. Lancet Gastroenterol Hepatol 2020;5:276-84.

Received: 01 April 2020; Accepted: 20 April 2020; Published: 30 December 2020.

doi: 10.21037/dmr-20-36

View this article at: http://dx.doi.org/10.21037/dmr-20-36

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 (TNFα) 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 TNFα 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-TNFαs, but evidence suggests an increased risk of skin cancer, including melanoma, in patients exposed to a combination of thiopurines and anti-TNFα therapies (10-12). IBD patients with a history of cancer have therefore typically been excluded from anti-TNFα 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-TNFα 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-TNFα 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-TNFα 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-TNFα therapy (16). Furthermore, the population-based study by Silva-Fernández *et al.* concluded that patients with RA and prior malignancy who received an anti-TNFα 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-TNFα 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-TNFα therapy. Participants on anti-TNFα therapy were matched by sex, disease type and cancer type with 10 controls who were not treated with anti-TNFαs. The primary outcome was development of new or recurrent cancer. Overall, 434 patients with immune-mediated disease treated by anti-TNFα 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-TNFα 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-TNFα 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-TNFα 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-TNFα therapy and goes some way to ease the difficult decisions around using these medications in this context.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Digestive Medicine Research*. The article did not undergo external peer review.

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-20-36). The author has no conflicts of interest to declare.

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.

References

1. Available online: https://www.crohnsandcolitis.org.uk/about-inflammatory-bowel-disease
2. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet 2015;386:1825-34.
3. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541-9.
4. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006 Feb;130:323-33; quiz 591.
5. Sandborn WJ, Hanauer SB, Rutgeerts P, et al. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56:1232-9.
6. Lawson MM, Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2006;(3):CD005112.
7. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462-76. Erratum in: N Engl J Med. 2006 May 18;354:2200.
8. Nielsen OH, Seidelin JB, Munck LK, et al. Use of biological molecules in the treatment of inflammatory bowel disease. J Intern Med 2011;270:15-28.
9. Available online: https://www.cancerresearchuk.org/health-professional/cancer-statistics-for-the-uk#heading-Zero
10. Farrell RJ, Ang Y, Kileen P, et al. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. Gut 2000;47:514-9.
11. Armstrong RG, West J, Card TR. Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study. Am J Gastroenterol 2010;105:1604-9.
12. Long MD, Martin CF, Pipkin CA, et al. Risk of melanoma and nonmelanoma skin cancer among patients with inflammatory bowel disease. Gastroenterology 2012;143:390–399.e1.
13. Axelrad J, Bernheim O, Colombel JF, et al. Risk of New or Recurrent Cancer in Patients With Inflammatory Bowel Disease and Previous Cancer Exposed to Immunosuppressive and Anti-Tumor Necrosis Factor Agents. Clin Gastroenterol Hepatol 2016;14:58-64.
14. Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA 2006;295:2275-85. Erratum in: JAMA. 2006 Jun 7;295(21):2482.
15. Mariette X, Matucci-Cerinic M, Pavelka K, et al. Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. Ann Rheum Dis 2011;70:1895-904.
16. Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. Arthritis Rheum 2007;56:1433-9.
17. Silva-Fernández L, Lunt M, Kearsley-Fleet L, et al. The incidence of cancer in patients with rheumatoid arthritis and a prior malignancy who receive TNF inhibitors or rituximab: results from the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis. Rheumatology (Oxford) 2016;55:2033-9.
18. Dignass A, Van Assche G, Lindsay JO, et al. The second European evidence-based Consensus on the diagnosis and management of Crohn's disease: Current management. J Crohns Colitis 2010;4:28-62. Erratum in: J Crohns Colitis 2010 Sep;4(3):353. Dosage error in article text.
19. Lichtenstein GR, Hanauer SB, Sandborn WJ, et al. Management of Crohn's disease in adults. Am J Gastroenterol 2009;104:465-83; quiz 464, 484.
20. Bernstein CN, Fried M, Krabshuis JH, et al. World Gastroenterology Organization Practice Guidelines for the diagnosis and management of IBD in 2010. Inflamm Bowel Dis 2010;16:112-24.
21. Waljee AK, Higgins PDR, Jensen CB, et al. Anti-tumour

necrosis factor-α therapy and recurrent or new primary cancers in patients with inflammatory bowel disease, rheumatoid arthritis, or psoriasis and previous cancer in Denmark: a nationwide, population-based cohort study. Lancet Gastroenterol Hepatol. 2020;5:276-84.

doi: 10.21037/dmr-20-36
Cite this article as: Phillips J. Mounting evidence that anti-tumour necrosis factor-α therapy does not increase the risk of new or recurrent cancer. Dig Med Res 2020;3:106.