EDITORIAL

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Tumor necrosis factor-α inhibitor use in patients with malignancy: is it safe?

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Article: Safety of tumor necrosis factor inhibitor use in patients with concomitant malignancy **(Intest Res 2020;18:282-288)**

Tumor necrosis factor (TNF)-α is achieved by macrophages and activated T-cells with the aim of necrotizing tumor cells. Therefore, the inhibition of TNF-α can theoretically be linked with cancer development or progression.[1] Several studies have been performed to assess the risk of cancer development associated with TNF-α inhibitors (TNFis) used in IBD since 1995. Because the majority of patients treated with TNFis had also used thiopurine, it is difficult to discern the effect of TNFis alone. Based on the first meta-analysis from controlled studies of infliximab therapy in patients with CD, there was no difference found in the cancer incidence among the patients treated with infliximab and placebo.[2] Similar findings have been observed in a more recent pooled analysis of 22 randomized controlled trials, where no significant difference between the TNFi and placebo in the incidence of cancer diagnosed within the first treatment-year was reported.[3] As for adalimumab, a pooled analysis data of IBD suggested no increased risk of adalimumab-related cancer development existed, although there was significantly increased risk with both use of adalimumab and immunomodulators.[4] Taken together, there have been no solid evidence available supporting TNFis alone increase the overall risk of cancer development.

During the TNFi therapy of IBD patients with a history of malignancy, there could be raised 3 questions. First, evidence-based, what effects do TNFis use in IBD have on the malignancy progression? Second, practically, how should TNFis use in IBD be managed in patients with a previous or recent history of malignancy? Third, practically, how should TNFis use in IBD be managed in patients with a newly diagnosed malignancy?

Considering the first question, there was a research assessing IBD patients with a recent within 5 years' history of malignancy and use of TNFis. Cancer-free survival rate at 5 years was 72%.[5] In addition, a multicenter study in the United States assessing IBD patients having a previous malignancy history and use history of TNFis.[6] TNFi use was not associated with developing a recurrent or new cancer as compared with no users. Contrastingly, a predictive model in the United States suggested that a second cancer could be increased elevenfold following 9.5 year-TNFi use.[7] Taken together, in IBD, there was no solid and clear evidence of relationship between increased risk of developing a new or recurrent cancer and TNFi use.

With regard to the second question, however, the effects of TNFis on malignancy are unpredictable. Infliximab has been effectively used to treat ipilimumab-associated severe colitis without changing the clinical outcome of the melanoma.[8] However, this was from a small number of patients with relatively short follow-up time. Furthermore, there was a case of lung cancer developed during adalimumab use in IBD and regressed after adalimumab discontinuation.[9] Taken together, TNFi should be discontinued until cancer therapy completion, for 2 years

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or for 5 years in high risk of recurrence after completion of cancer treatment.

To answer the third question, in the present issue of *Intestinal Research*, Phan et al.[10] reported findings suggesting TNFis may be safely used in select inflammatory disease patients including IBD patients with concurrent cancer. This study appears to be the first to compare these 2 strategies of TNFi use, stopping or continuing at the time of malignancy diagnosis. As part of their research, Phan et al. highlighted survival and recurrence findings at 1, 2, and 5 years following diagnosis of malignancy with and without TNFi use. Among 36 cases and 72 controls, surviving patients at 1, 2, and 5 years were 89%, 86%, and 81%, and 90%, 87%, and 73%, respectively. Separately, among cases and controls, instances of recurrence at 1, 2, and 5 years were 8%, 14%, and 17%, and 3%, 7%, and 10%, respectively. In this matched cohort study, there was no relationship between TNFis use and cancer recurrence and overall survival. However, this study comprised a relatively small number of patients and very heterogeneous inflammatory diseases. Therefore, decisions for the optimal timing of TNFi use in IBD and inflammatory disease around the time of malignancy diagnosis should still be made in case-by-case base with consulting oncologists and considering the activity of inflammatory diseases.

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CONFLICT OF INTEREST

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