

No Significant Association between Malignancy and Anti-TNF- α Agents in Crohn's Disease

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Risk of malignancy associated with bowel inflammation associated with Crohn's disease, in particular colorectal cancer and small bowel adenocarcinoma, is an important concern for Crohn's patients. Medical therapies for Crohn's disease, in particular thiopurines, are associated with increased risks of certain malignancies, in particular lymphoma and non-melanoma skin cancer (NMSC). Since the introduction of infliximab, tumor necrosis factor (TNF) α antagonists have replaced immunomodulators and become the mainstream treatment for Crohn's disease [1]. Unfortunately, the long-term safety of TNF- α antagonists is difficult to measure, in particular due to the lack of long-term safety data from randomized clinical trials.

Recently, Lichtenstein, et al. reported the long-term risk of malignancy associated with drug therapies in 6,273 Crohn's patients from the TREAT registry [2]. The Crohn's Therapy, Resource, Evaluation, and Assessment Tool (TREAT) registry is a prospective large cohort study on long-term outcomes of CD treatments treated in both community and academic settings in North America. Patient data was collected at scheduled semi-annual visits, during which adverse events including malignancies were reported.

The authors aimed to examine the relationship between infliximab use and malignancy risk. Of the 6,273 patients studied, 3,420 were exposed to infliximab and followed on average for 5.2 years. There were 14 lymphomas, 53 NMSCs, 135 solid tumors, and a total of 207 malignancies reported in the TREAT registry. The crude cancer incidences were similar between infliximab-treated and other-treatment-only patients (0.64 vs. 0.71 per 100 patient-years, $p=0.48$). Not surprisingly, patients treated with infliximab were on average 4.4 years younger, had more severe Crohn's disease, and were commonly treated with other medications including steroids and other immunosuppressants. In multivariate Cox regression analysis, age (hazard ratio [HR] 1.59/10 years), disease duration (HR 1.64/10 years), and smoking (HR 1.38) were independently associated with the risk of malignancy (all $p<0.05$). On the other hand, neither immunosuppressive therapy alone, infliximab therapy alone, nor their combination was associated with the risk of malignancy after controlling for other risk factors.

The authors also compared the rates of malignancy in the TREAT registry with those in the general population based on the SEER database. They found no significant increase in incidence in any malignancy category. Finally, the authors carried out an exposure-based analysis and did not find any significant increase in malignancy risk associated with the number of infliximab infusions. They concluded that there was no significant association between infliximab and malignancy in the TREAT registry.

This study has several important limitations. As an observational study, there was inherently selection bias in the choice to use infliximab, as shown by more severe Crohn's disease in patients treated with infliximab. However, such bias likely led to an overestimate of malignancy risk associated with infliximab use. A significant number of patients dropped out or discontinued infliximab in the registry. Consequently, there was a great variety in the number of infliximab

infusions given. The rarity of malignancy led to wide confidence intervals and made it difficult to estimate malignancy risk by cancer type. Finally, some malignancies may take longer than the average followup of 5.2 years to manifest.

Despite the above limitations, the fact that this largest study available to date found no significant malignancy risk associated with infliximab in Crohn's disease is reassuring. Any malignancy risk associated with infliximab in Crohn's disease, if existent, is likely small therefore could not be quantified even with the large sample size of the TREAT registry. It is also possible that by inducing remission of Crohn's disease, anti-TNF- α agents may have chemoprotective effect and reduce the risk of malignancy associated with inflammation over time. We keenly await longer-term and better-quality safety data of infliximab and other anti-TNF- α agents to help guide the risk/benefit tradeoffs in managing Crohn's disease.

References

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