The Risk of Malignancy Associated with the Use of Biological Agents in Patients with Inflammatory Bowel Disease

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KEYWORDS

• Malignancy • Lymphoma • Skin cancer • Biologics • Inflammatory bowel disease

KEY POINTS

- The risk of lymphoma and skin cancer with anti–tumor necrosis factor (anti-TNF) therapy is largely driven by the use of concomitant immunomodulator therapy, particularly thiopurines.
- The risk of lymphoma and skin cancer with newer biologics seems to be similar to that seen with anti-TNF therapy, but this is largely based on either non–inflammatory bowel disease (IBD) data or IBD data with short follow-up.
- Tofacitinib has a measurable risk of malignancy when used in patients with rheumatoid arthritis, and further long-term data are needed in patients with IBD.
- In patients at particular risk for developing a malignancy while on therapy, there should be an effort to focus on modifiable risk factors.
- The optimal approach to the use of biologics in patients with IBD with a previous history of malignancy remains unclear.

INTRODUCTION

The pathogenesis of inflammatory bowel disease (IBD) is multifactorial and involves a complex interaction between genetic, environmental, microbial, and immune factors.[1] The ensuing pathologic response affects both the innate and adaptive immune systems, with the net result of these cellular mechanisms being granulocyte

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accumulation, cytokine production, and intestinal inflammation.[2,3] This complex immune response has provided the opportunity for the development of biological agents that target specific components of the immune cascade.[4] These biological drugs have dramatically changed the manner in which the treatment of IBD is approached and the outcomes that may be expected. Despite the proven efficacy of these agents and the shifting of treatment goals toward early aggressive use of these drugs,[5–7] concerns surrounding toxicity have posed a significant emotional barrier to their use. Infectious complications remain the most common side effect, but the fear of developing cancer poses the greatest obstacle for patients and providers to overcome.[8–10]

Patients with IBD are at an increased baseline risk for intestinal and extra-intestinal malignancies,[11–13] but the 2 cancers that have gained the most attention are lymphoma and skin cancer. Although there are some conflicting data,[12,14] several studies suggest that IBD alone is not associated with an increased risk for lymphoma.[11,15,16] In contrast, there seems to be a clear association between IBD and the development of melanoma and nonmelanoma skin cancers (NMSC).[13,17,18] There is also much evidence implicating IBD-related medications, particularly thiopurines, in the development of these malignancies.[18–21] It is difficult to determine the risk of malignancy with biologics on their own, because most patients with IBD treated with biologics have also previously been exposed to thiopurines.

In this review, the available evidence regarding the risk of malignancy when using biological agents for the treatment of IBD are highlighted, with a particular focus on lymphoma and skin cancer. This risk is compared with that seen with other treatment options in IBD and with the general population. The approach to managing these medications in patients who have a history of malignancy is further highlighted. We anticipate that this review will help providers better understand how best to broadly approach the difficult conversation of biological therapy and cancer with their patients.

ANTI–TUMOR NECROSIS FACTOR THERAPY

Risk of Lymphoma

The hallmark of active IBD is infiltration of the lamina propria by innate (neutrophils, macrophages, dendritic, and natural killer T cells) and adaptive immune cells (B and T cells). The increased number of these activated cells in the intestinal mucosa leads to enhanced local levels of proinflammatory cytokines, which play important roles in the interaction between immune and nonimmune cells.[22] One of these cytokines, tumor necrosis factor α (TNF-α), has been shown to play a key role in the pathogenesis of IBD, and has therefore served as the prototypical target for biologics in both Crohn disease (CD) and ulcerative colitis (UC). Around the time that infliximab was approved from use in CD, there was already increasing concern over a potential increase in risk of lymphoma with these agents.[23] Since then, the evidence surrounding the potential association between anti-TNF therapy and lymphoma occurrence has increased significantly.

Initial attempts at understanding the risk of lymphoma with anti-TNF therapy used pooled analyses of randomized controlled trials (RCTs). The first meta-analysis to look at this subject[24] pooled data from 21 RCTs and assessed the efficacy and safety of anti-TNF agents for the treatment of CD. This study examined 3341 patients exposed to anti-TNF with a median follow-up period of 24 weeks per patient and did not find an increased risk for lymphoma occurrence with anti-TNF use. In most of these RCTs, many of the controls also had some exposure to anti-TNF therapy. The investigators performed a sensitivity analysis of studies with unexposed controls, but this was an exploratory subanalysis and was likely underpowered to address this