1. **Infliximab and adalimumab have comparable efficacy and safety in UC**

Infliximab and adalimumab are the most commonly used anti-TNF agents in UC. Although clinical trial data show similar efficacy, comparative trials have not been performed. To study the real-world comparative effectiveness and safety of these two biologics, the authors have used data from a large administrative database covering about 100 M people in the US. Diagnoses, medications, comorbidities and outcomes were extracted, using diagnostic and procedure-associated codes. 1,400 bio-naïve UC patients were identified, of which 1,112 were started on IFX, and 288 on ADA. Similar proportion of patients in each group received concomitant IMM (32%) or steroids. After adjusting for a number of baseline variables, there was no difference between the IFX- and ADA-treated patients in terms of any hospitalization, UC-related hospitalization, steroid use or serious infections. The rate of surgeries was very small in both groups. Using a different statistical approach, the use of steroids after starting the biologic was lower in the IFX group compared to the ADA group. The findings were robust when the analyses were limited to observations after 2012 (the year of ADA approval for UC).

**Comments:** although the investigators were unable to account for disease severity in their analyses, the results of this study provide “real-life” evidence of equivalent efficacy of IFX and ADA in patients with UC who are bio-naïve. Other potential confounders that were not accounted for include smoking, body weight and medication compliance. Absent a head-to-head control trial of the two biologics, these observations provide a reasonably good support for treatment decisions in clinical practice.


2. **Safety of vedolizumab for UC and Crohn’s disease**

Vedolizumab (VDZ) is a gut-selective trafficking inhibitor humanized monoclonal antibody, that blocks the migration of T-cells from the blood to the inflamed intestinal mucosa, and thus is effective for the treatment of both UC and Crohn’s disease. Given its recent launch, only limited safety data is available. Investigators have performed a safety analysis using pooled data from 6 clinical trials (2 UC, 2 CD and 2 combined open-label long-term trials) encompassing over 2,800 patients who received at least one dose of VDZ, contributing a total of 4,811 patient-years of VDZ exposure. The control group included 504 patients who received only a placebo in addition to their baseline drugs. Exposure-adjusted incidence rates of all AEs and serious AEs, were...
lower with VDZ compared with Pbo. No increased risk of serious infections was associated with VDZ. There was a higher rate of gastroenteritis with VDZ, as well as, a trend for Clostridium infections but this did not reach statistical significance. No cases of PML were seen among VDZ users. Extrapolation modelling using natalizumab risk predicted that 6-7 cases would have occurred if the risk of PML was similar between VDZ and natalizumab. Independent risk factors for serious infections in the entire cohort were prior anti-TNF failure, concomitant narcotic or steroid use and young age. The number of malignancies including GI cancers was too small to detect an association. The rate of antibody formation with continuous use was 4% but increased to 18% with episodic use. Concomitant IMM therapy reduced the risk of anti-VDZ antibodies. Infusion reactions were uncommon.

Comments: Based on its mechanism of action, VDZ should be one of the safest biologic drugs available on the market. However, real world safety data is lacking. The current study provides evidence supporting the safety claims for VDZ, including PML which was a feared complication given its similarity with natalizumab. This was further confirmed in post-marketing studies. Some limitations are present in this study including the short duration of follow-up for the majority of patients. Uncommon side-effects and particularly malignancies cannot be adequately evaluated in short-term studies. In fact, the risk of lymphoma and particularly hepatosplenic T-cell lymphoma with combination anti-TNF-IMM therapy was only revealed after several years of clinical use.


3. Safety of immunosuppressive therapy after cancer diagnosis

Immunosuppressive drugs are the foundation of medical therapy for a number of immune-mediated conditions including IBD. The benefits of IS drugs need to be balanced against possible risks, including malignancy. With improving results in treating cancers, patients with IBD who develop a malignancy are increasingly faced with the dilemma of balancing risks, and benefits of continuing or restarting IS drugs including; impaired immune surveillance, facilitation of oncogenic viruses or perhaps, and direct mutagenic effect. There is limited data to support clinical practice in this field. In this paper, investigators have performed a systematic review with meta-analysis to identify the rates of incident cancers (new or recurrent) in individuals with chronic immune-mediated diseases who were treated with IS therapy after a prior malignancy. After extensive literature review, the authors selected 16 unique studies who satisfied quality criteria for inclusion, of which, about half included patients with IBD. The pooled overall analysis included almost 11,702 people contributing 31,260 patient-years of follow-up after prior cancer diagnosis. Among these, there were 1,698 instances of new or recurrent cancers. There was no significant difference in the rate of incident cancers among people on no IS therapy, IMM therapy (thiopurines or methotrexate), anti-TNF therapy or combination (average 35 cases/1000 p-y). In subgroup analyses, there was no difference in incidence between new (different cancer, different location) and recurrent cancers, different immune-mediated disorders (IBD, RA, psoriasis) or different IMM (thiopurines vs. Mtx). The only significant difference was in the incidence rate of recurrent skin cancer (NMSC) with IMM
vs. no treatment (72 vs. 51 cases/1000 PY). No difference was seen with any other solid organ cancer including lymphoma. In comparative studies, there was a slightly lower rate of incident cancers with anti-TNF compared to IMM therapy (when including skin cancers). The results were robust after multiple sensitivity analyses showing no difference in the risk of incident cancers when IS was initiated, before or after 6 years after the index cancer diagnosis.

Comments: There are several limitations to this meta-analysis including:

- Major heterogeneity between studies;
- Lack of information regarding the aggressiveness of the cancer (patients with high-risk cancers are less likely to survive or be treated with IS therapy of any kind except for, perhaps 5-ASA and steroids);
- No information on IBD subtype or severity;
- Lack of information on steroid use;
- Dose or duration of IS therapy;
- Prevalence of smoking, etc.

The inclusion of non-melanoma skin cancer can also introduce a major bias as these cancers are relatively easy to detect and treat, and often do not require adjustment to therapy. Also, despite the attempt to stratify patients based on the duration of the drug ‘holiday’ the study was unable to tease out a ‘safe’ interval for IS drug initiation after cancer therapy. This is likely dependent of course, on the nature, histology, and risk of the index cancer. However, overall the results of this study are reassuring at least in regards to IS therapy in IBD patients with malignancies who have a good prognosis and in whom survival is felt to be at least 3 years after cancer diagnosis. Further prospective studies are needed to further define the risks and benefits of this strategy.