1. Drug therapy and the risk of cancer in Crohn’s disease

Under normal circumstances, immune surveillance has an important role in the prevention and containment of certain cancers. Therefore, immunosuppressive drugs such as azathioprine or methotrexate and particularly anti-TNF alpha biologics (TNF = tumor “necrosis” factor) theoretically could increase the risk of cancer in patients with IBD. To examine this association, investigators conducted an analysis using the TREAT registry, which is a prospective cohort study examining long-term outcomes in of Crohn’s disease treatment. This registry is supported by the manufacturer of infliximab (IFX) and was designed to include at inception equal number of patients on IFX and “other” treatments (such as 5-ASA, steroids and immunomodulators - IMM). Adverse events were voluntarily reported by participating gastroenterologists on a regular basis but not ascertained. In this paper, the authors review the incidence of malignancies in this cohort and compared it with the expected rate of cancer in the general US population (obtained from the SEER registry). Data was available for 6,273 patients followed until 2010 (average 5 years and eventually 54.5% IFX treated). Only 32% of patients in the “other treatment” group received IMM vs. 52% in the IFX group. Patients in the latter group also had more severe disease. There was no difference in the rate of neoplasia diagnosis between users of IFX (alone or in combination with IMM) and the other treatment group both overall and for any specific malignancy category (RR 0.9, p=0.46). In multivariate analyses, baseline age (HR=1.59/10 years), disease duration (HR=1.64/10 y) and smoking (HR=1.38) were independently associated with the risk of malignancy. When compared to the SEER database, breast cancer and prostate cancer were less common in the TREAT registry (the latter only for the “other” treatment group). Lymphoma rates were also higher in the IFX- and IMM-treated groups compared to SEER but this difference did not reach statistical significance.

Comments: The good news emanating from this paper is that the risk of cancer in Crohn’s disease patients treated with biologics alone or in combination does not seem to be substantially increased compared to the general population. The study has several major limitations, however, of which the most important ones are lack of power and under-reporting. Based on the power calculations, the study was only able to detect a significantly increased risk of lymphoma if the relative risk exceeded 4.75. Thus, the present findings are likely a type 2 error. Several other studies have shown the risk of lymphoma in anti-TNF users to be between 2-3 fold which is “under the radar” for the present study. Similar arguments exist for non-melanoma skin cancer, the other sentinel cancer associated with biologics. It is likely that far more skin cancers developed in this cohort than reported by the participating gastroenterologists in this study (all adverse events were voluntarily reported and not ascertained). More than half the patients were lost to follow-up by the end of the survey period which is an important confounder. Of the 3 risk factors identified here, age, disease duration
and smoking, the latter is the only modifiable one and should serve as another argument for physicians to counsel their patients regarding smoking cessation.

Source:


Two anti-TNF agents are effective and approved for treatment of UC (infliximab and adalimumab). In the most recent issue of Gastroenterology, investigators report on two multi-center randomized trials investigating a fully human, injectable anti-TNF drug, golimumab (GMB) for induction and maintenance of response in moderate-severe, steroid-dependent UC or who failed IM therapy. The induction trial(s) (called PURSUIT-SQ) included a phase 2 dose-finding part and a phase 3 part totaling 1,064 patients with UC who were treated with GMB every 2 weeks at doses of 100/50 mg, 200/100 mg and 400/200 mg SQ. At week 6, significantly higher proportions of patients in the GMB 200/100 and 400/200 achieved clinical response compared to placebo (51% vs. 30%) with no significant difference between the two doses of GMB. Remission rates were 18% for either GMB dose and 6.4% for placebo. However, there was a direct correlation between the serum golimumab concentrations at week 6 and the change from baseline in the Mayo score and rates of clinical response and remission. Only 3 patients (0.4%) developed antibodies to GMB, neither one of which was neutralizing. There was no difference in the rate of adverse events between the GMB and placebo groups although one patient receiving the higher induction dose of golimumab died of peritonitis and sepsis after surgical complications related to an ischiorectal abscess. In the maintenance trial (PURSUIT-M), patients who responded to induction therapy with GMB in PURSUIT-SQ were randomized to receive either 100 or 50 mg golimumab SQ every 4 weeks and were followed up through week 54. The response (50% vs. 31%), remission (28% vs. 16%) and mucosal healing rates (42% vs. 27%) were significantly higher in the group receiving 100 mg golimumab vs. placebo but there was no difference between the 50 mg and 100 mg every 4 week doses. Again the study found a positive correlation between GMB trough levels and response rates. There were slightly more adverse events with the higher GMB dose but the serious infection rates were similar. There were 4 cases of tuberculosis in the GMB group of which one died.

Comments: Golimumab provides a third option for patients with moderately severe ulcerative colitis with rates of response and remission similar to previous anti-TNF biologics. Although the authors claim that the methodology of the study and particularly the definition of response and remission (continuous rather than at designated time points) was more rigorous compared to other studies, the overall clinical and biological effect (mucosal healing) seem quite similar. I suspect clinicians will prefer to use intra-venous biologics for patients hospitalized for severe UC
either by convenience or by force as most injectable biologics are not on hospital formularies. Otherwise golimumab can be considered as a first or second line drug in patients with UC who fail standard therapy or have a secondary loss of response to another biologic. The question that remains unanswered is the lack of a dose effect for both induction and maintenance. It is possible that there is a ceiling effect for response rates which is closer to the lower dose. On the other hand the serum trough levels showed a nice correlation with the rates of response which suggest that, like the other biologics, the dose of GMB could be individualized if levels become available for clinical use. It is also unclear from this study whether combination therapy is superior to monotherapy although patients receiving immunomodulators had lower incidence of antibodies to GMB (1% vs. 4%). Interestingly, only 2/3 of the antibodies were neutralizing, which means that the presence of antibodies to GMB is not always relevant; this has been previously speculated based on experience with previous anti-TNF biologics.

**Sources:**


3. **Infliximab alone or in combination with methotrexate for Crohn’s disease.**

The argument of biologic mono vs. combination therapy with thiopurines for Crohn’s disease has been well addressed in the SONIC trial published a few years ago. Now, many years after its actual completion, the methotrexate (MTX) sister study (COMMIT) finally came out in print. In this study, 126 patients with Crohn’s disease who were recently started on steroids for active symptoms were randomized to receive either IFX alone or in combination with an escalating dose of methotrexate (from 10 to 25 mg weekly) and were followed through week 50. There was a forced steroid taper by week 14. All patients were pretreated with steroids prior to their IFX infusion. There were no significant differences in the rates of treatment failure between groups at the end of the study. 76% of patients achieved steroid-free remission at 14 weeks and 56% at 50 weeks. Patients receiving MTX were less likely to develop antibodies to IFX (4% compared to 20%) and had higher serum IFX trough levels. There was no difference in the rate of adverse events.

**Comments:** The remission rates in this trial are the highest of any biologic trial in patients with CD. On the other hand, the study showed no difference between the monotherapy and combination therapy arms. We have to acknowledge the fact that the primary endpoint was subjective (CDAI) and there was no data on mucosal healing or calprotectin. However there was no difference in CRP levels throughout the study. So how can these results be reconciled with
those of SONIC? First, the study design and patient populations were different. All patients in the COMMIT trial were induced with steroids and a substantial number were in clinical remission by the time of randomization, so they may have had milder disease. In other words this can be considered a steroid-withdrawal trial whereas SONIC was a typical induction of remission trial. The patients also received pre-infusion steroids throughout the study period. The definition of treatment failure was also somewhat arbitrary and no true “placebo” arm was included (or a methotrexate monotherapy arm). That said, a previous open-label study evaluating top-down therapy (D’Haens et al. – Lancet ’08) also showed steroid-free remission rates of 60% at 26 and 54 weeks in patients receiving early combination therapy with IFX and azathioprine. I think it is premature to dismiss methotrexate as a combination agent in patients who are starting biologic therapy and particularly in young males where the risk of combination therapy with thiopurines is perceived to be higher. However, the finding that induction therapy with steroids may boost the effect of anti-TNF drugs when used as maintenance therapy is intriguing and deserves further study.

Source:

In other news:
Adalimumab combined with ciprofloxacin superior in perianal fistulas
A small randomized double-blind placebo controlled trial in 76 CD patients with active perianal fistulas found that adalimumab combined with ciprofloxacin 500 mg twice daily for 12 weeks was superior for reduction in fistula drainage and fistula closure at 12 (71% for combination vs. 47% Ada alone) but not at 24 weeks. In conclusion, combining an anti-TNF agent with an antibiotic seems to be a superior strategy albeit short-lived (only for the duration of co-administration). The more interesting practical question is whether intermittent antibiotic therapy (such as 1 in 4 weeks) will have the same benefit and that can be sustained.

Source:

Tofacitinib fails in Crohn’s disease: is it the drug or the investigators’ bust?
In a phase 2 trial of patients with moderate-severe Crohn’s disease conducted at 48 centers in 12 countries, tofacitinib (an orally administered JAK inhibitor) failed to show a difference in response compared to placebo. However, the placebo response and remission rates in this population with moderate-to-severe disease were 47% and 21%. These placebo response rates are virtually unheard of in practice or clinical trials in patients with active disease receiving placebo. There were other discordant results as well, for instance there was a trend toward a
dose-effect association for clinical response but an inverse correlation between dose and clinical remission which is counterintuitive. Therefore one has to question the veracity of the study proceedings and the study oversight. Importantly, the 15 mg dose of tofacitinib significantly decreased the levels of CRP and fecal calprotectin more than placebo. Furthermore, tofacitinib was shown to be effective for induction of response and remission in UC, although this does not imply that it should be effective for CD as well. It is likely that a phase 3 study will be pursued with more rigorous study methodology.

Source:

**REMINDER: The 2nd Annual Virginia Mason IBD Update will take place on March 14th, 2014 at the Volney Auditorium in Seattle. Please visit our website to register.**