1. Risk of a second non-melanoma skin cancer among immunosuppressive drug users

Imunosuppressive drugs used to treat RA and IBD can increase the risk of skin cancer (particularly squamous-type) through photosensitization (such as thiopurines and methotrexate), decreased immune surveillance (anti-TNF), or by promoting the growth of onco-viruses. There is limited data on the risk of a second NMSC in patients using these medications. These investigators performed a retrospective cohort study among Medicare recipients with RA and IBD from 2006 through 2012. The analysis included almost 9,500 individuals (more than 2/3 with RA) of which, 13% developed a second NMSC 1 year or more after the first one (incidence rate of 6%/year among both RA and IBD cohorts). Both methotrexate (HR 1.60) and anti-TNF drugs (HR 1.49) were associated with an increased risk of a second skin cancer, but interestingly thiopurines were not. The hazard risk of a second NMSC increased with longer MTx exposure from 1.1 after < 1 year to 1.59 after 3 years or more. Cumulative corticosteroid exposure was not significantly associated with a risk of second NMSC in RA patients.

Comments: This study is likely to create quite a bit of stir in the world of both rheumatologists and gastroenterologists, as it has long been held that methotrexate is a safer option for IMM therapy in patients with a history of skin cancer, whereas this study shows quite the opposite. Certainly, a number of confounders may be present starting with the fact that the Medicare population in this study may not be representative of the general US population. Similarly, there is no information about the dose and duration of IS therapy before the ‘first’ skin cancer which may have biased the risk of recurrence. There is also the risk of misclassification of some recurrent skin cancers as being ‘second’ cancers. The most surprising fact is the lack of association of a second NSMC with thiopurine use, which is very difficult to explain and is likely due to other confounders. Nevertheless, this information is certainly useful for practitioners for risk estimation and patient counseling.


2. How much risk are IBD patients willing to accept to achieve remission?

The benefits and risks of IBD medications are very important for the process of selecting the appropriate medical therapy for an individual patient. Patient and physicians’ perception of risk
often differ and there is conflicting information about the patients’ tolerance level for side-effects in order to achieve benefits from a specific drug. Investigators from a single referral center performed a survey on 374 patients with IBD (202 valid responders) using a ‘discrete choice experiment’ – i.e. subjects were asked to choose among a few pre-determined risk and reward values rather than picking responses from a range. Competing hypothetical treatment models and outcomes were utilized to assess the maximum acceptable risk (MAR) of medication-related SAE that would offset the perceived benefit of avoiding a future IBD relapse. The majority of patients had UC and were in remission at the time of completing the survey. To delay a flare by 5 years, patients were willing to accept up to a 28% chance of having a serious infection and 1.8% chance of having lymphoma. Interestingly, patients with self-reported IBD in remission had double the risk tolerance of patients with self-perceived active disease. For instance, in order to maintain response for 5 years, patients in remission were willing to accept a MAR of almost 40% for serious infections and 2.8% of lymphoma, compared to 21% and 1.3% respectively in patients with active disease. UC patients placed a greater importance on avoiding relapses compared to CD patients.

Comment: Patients in this study appear to be willing to accept fairly high risks of serious infections and lymphoma to maintain remission, in virtually all scenarios much higher than actually encountered in real life. Whether these results obtained in a referral center are generalizable is unclear. The average age was 50 and the vast majority of patients had some college education, including 30% with post-graduate studies. As most patients in this cohort have never experienced a serious adverse event and none experienced lymphoma, these high response rates may be due to “ignorance bias”. The vast majority of patients were in remission but interestingly, patients with active disease were less likely to accept risk to achieve and maintain response. This may be explained by the fact that either ‘active’ patients had mild disease, had adapted to living with symptoms, and/or experienced failure with a number of drugs. A trend towards instant gratification is also evident; patients discounted heavily maintenance of response > 5 years compared to 1-5 years. This paper is very useful for practitioners to gauge their treatment recommendations based on some objective evidence of risk tolerance by patients.


3. More data supporting calprotectin as a predictor of disease response in UC

Several prospective and retrospective studies have demonstrated that fecal calprotectin (FC) is a reliable marker of intestinal inflammation in both UC and CD. Whether measurement of FC can be used as a surrogate endpoint in clinical trials with pharmacologic agents, is unknown. Tofacitinib is a JAK inhibitor which has demonstrated efficacy in rheumatoid arthritis as well as in a phase-2 clinical trial in UC. In the latter, treatment with tofacitinib was associated with significant improvement in clinical and endoscopic outcomes as well as a reduction in FC at 8 weeks. This study was a post-hoc analysis of data from this clinical trial, which assessed the relationship between FC concentrations and clinical and endoscopic responses. Overall, 194
patients received at least 1 dose of the study drug and about 80% had both baseline and week 8 FC data. Median FC concentrations were significantly lower in patients who achieved clinical response. Remission and endoscopic remission compared to non-responders at 8 weeks. Using ROC analyses, a cutoff FC concentration of 150 mg/kg had a sensitivity and specificity of 68% and 79% for clinical remission, and 79% and 75% for endoscopic remission. The corresponding PPV and NPV were 0.57 and 0.86 for clinical remission and 0.39 and 0.94 for endoscopic remission. There was a significant dose response curve for FC concentrations to tofacitinib, which correlated fairly well with clinical and endoscopic remission.

Comments: Although a post-hoc analysis, this was the first study to evaluate the diagnostic performance of fecal calprotectin in a clinical trial setting. It showed a strong correlation between FC concentrations, clinical and endoscopic outcome measures. In this study, a cut-off value of 150 mg/kg seemed to have the best accuracy in correctly predicting clinical and endoscopic outcomes. The main potential bias in this study is the reference standard, whether clinical or endoscopic. Since there was no central reader for the endoscopic assessment, a source of bias cannot be excluded especially given the substantial placebo response rates (42% response, 10% remission and 33% mucosal healing). Of note, 10% of patients had normal FC at enrollment despite having at least left-sided disease. Since FC has a slower dynamic curve compared to other biomarkers (such as CRP), the 8-week endpoint may also be a bit too early. Longer, prospective studies will be able to provide a more definitive answer as to the ability of FC to accurately predict long-term outcomes in patients with both UC and CD.