1. **Timing of anti-drug antibody development in patients treated with infliximab.**

Drug level and antibody assays are available for clinical use. Patients with high anti-drug antibody levels and/or low biologic trough levels are less likely to have sustained response to infliximab which has been the most studied of the anti-TNF agents. In this study, the investigators measured the temporal evolution of anti-infliximab antibody (ATI) development in a non-blinded cohort of patients with IBD treated with infliximab (IFX) at a single medical center. They used “home-grown” assays for drug and antibody level measurement with an internal validation protocol based on a standard titration curve. The outcome of interest was clinical response which was based on the judgment of each individual clinician. Dose escalation and treatment intensification (addition of IMM) was allowed per clinical judgment. Each patient had on average of 9 serum samples drawn for the duration of the study and each was considered as an independent sample in some of the analyses. The vast majority of patients received combination therapy with a thiopurine. Overall 46% of patients developed ATI, of which half became positive in the first 6 weeks and 90% of ATI positive patients occurred in the first 12 months. There was a significant association between trough IFX and ATI levels and loss of clinical response although a threshold level could not be calculated due to a significant overlap. The investigators also noted that patients with high-level ATI were more likely to occur early and lose response compared to patients with low-level or “transient” ATIs.

**Comments:** The validity of this study is rather questionable given the modest methodology. Aside from the fact that the study was unblinded and used a subjective endpoint (clinical response), the mixing of paired with independent point estimates represents a major flaw. In fact, each patient was accounted for an average of 9 times for drug, antibody levels and clinical response sometimes as a responder other times as failure and switching “teams” at random. There is no information about steroid use and no drug-dose/trough level relationships are described. Therefore, I would interpret the results and conclusions of this work with a great deal of caution. However, what appears to be a valid finding here is that antibody development can occur early (50% by 6 weeks) and then drops substantially especially after one year of therapy, at least in IFX users. Combination therapy appears, again, protective even in patients on scheduled maintenance therapy. Therefore, it seems reasonable to use combination therapy in most IFX users for at least 1 year followed by monotherapy on a case by case basis. Of course, this issue has to be individualized based on each patient’s profile. The answer to the more important question regarding the threshold levels for IFX and ATI that predict loss of response has eluded these investigators. We can all figure out which patients are doing well without measuring drug levels but it is more difficult to determine if a patient’s loss of response is transient or definitive, related to ATI, low drug levels or an alternative mechanism (in those with
detectable IFX). It is entirely possible that a new approach is necessary to measure the actual biologic effect of a drug (equivalent to HCV titers in Hep C therapy) and not just simply pharmacokinetics. This hypothetical assay could then be applied not only to anti-TNF therapy but any other immunomodulator drug used in IBD. The currently available CRP is too rudimentary for this purpose.


2. **More evidence linking thiopurines with lymphoma in IBD.**

It is well known that the use of thiopurines (TP) is associated with an increased risk of lymphoma in patients who underwent organ transplant. However, data in patients using these drugs for treatment of IBD is controversial. Investigators utilized a nation-wide VA retrospective IBD patient database to estimate the risk of lymphoma in users of thiopurines (Aza and 6-MP) for treatment of ulcerative colitis (UC) over a period of 10 years. Using ICD-9 codes they identified almost 37,000 patients with UC of which 13% received TP for a median of one year. The incidence of lymphoma was 0.6/1000 among non-users compared to 2.3 in current TP users and 0.3 among previous users. The adjusted hazard ratio of lymphoma was 4.2 in users and 0.5 in previous users compared to never users. Also, the age-adjusted HR of lymphoma was 7.0 compared to the SEER database. There was an association between incidence of lymphoma and duration of therapy which became very significant after 4 years of use.

**Comments:** This is a very large study conducted within the largest health management system in the US. There are approximately 26 million veterans in this country of which about 1/3 obtain their medical care in the VA system each year (the other 2/3 are probably a mix or have private insurance). This study provides fairly convincing evidence of an association between thiopurine use and lymphoma in patients with UC. Particularly striking are the risk drop after stopping TP’s and the cumulative risk of lymphoma, both of which strengthen the likelihood of causality. Could the investigators have over-estimated the risk? Undoubtedly, this retrospective cohort is not representative of the US population and certainly not the IBD population. Patients were predominantly old males and there was no information on smoking, HIV and hepatitis C all known risk factors for lymphoma (marginal zone-type in the case of hepatitis C). Yet, one has to assume that there were fewer smokers among these patients compared to say Crohn’s patients. This is also not an inception cohort. Half the patients with UC in this study were “diagnosed” after the age of 60, while in most non-VA populations, the majority of patients are diagnosed with UC before the age of 30. While it’s true that 2/3 of UC patients have mild-moderate disease, this VA cohort seems to be rather super-mild. There was a minimum duration of only 1 month of VA enrollment required for eligibility. Only 14% of patients required VA-provided immune-suppressives, of which 50% for less than 1 year. There is no information on weight-
adjusted dosing for TP among users. Again, smoking may be “blunting the edge” of some UC patients in this population. On the other hand, as the authors pointed out, while the VA is a health-care system, it is definitely not an enclosed one. It is quite likely that patients with more severe disease phenotype or different risk profile, had most of their IBD care outside the VA system (often academic centers are conveniently located next door). It is unclear if the authors can account for outside prescriptions of any kind and in particular, biologics. Some patients may have been drawn into the VA system by symptoms consistent with lymphoma and the prospects of expensive care. The number of patients at risk tapered dramatically over time with less than 1,000 patients receiving drugs more than 3 years. A proportion of these patients were older than 65, the age when veterans become eligible for Medicare and can choose to have their healthcare transferred elsewhere along with their thiopurine prescription. This may introduce a substantial selection bias. Lastly, 1 out of 6 lymphomas in patients treated currently or previously with thiopurines developed in the colon. This is more suggestive of a chronic inflammation-related risk rather than one due to medication. With all these caveats, this study supports an association of thiopurine use with lymphoma and this risk has to be taken in consideration when using these drugs particularly in very young and very old male patients with IBD.


3. Risk of opportunistic infections in users of anti-TNF therapy.

Anti-TNF agents are extensively used in the treatment of IBD and other immune-mediated conditions. The decision to use these drugs relies on the balance of benefits v. side-effects and costs. Over the last 15 years, extensive experience has been accumulated on the benefits and risks of such agents from both clinical trials and post-marketing surveys. Two papers are presented here. The first one looked at the incidence of non-viral opportunistic infections (OI) in first-time aTNF users in a large cohort of patients assembled from multiple population databases including the Kaiser system in CA, two pharmaceutical assistance programs for the elderly, Tennessee Medicaid and US Medicaid/Medicare (the SABER database). The composition of this sample is thought to resemble the overall US population. The incidence of opportunistic infections in patients across all indications (RA, IBD, psoriasis, etc.) was compared among new anti-TNF users and patients initiating other disease modifiers (immunomodulators in the case of IBD) over approximately one decade. Among 33,000 new anti-TNF users, the investigators identified 80 non-viral OI, of which the most common ones were, surprisingly, Pneumocystis, Nocardia and tuberculosis, followed by Histoplasma, MAC and Salmonella. The overall incidence was 2.7/1,000 patient years in anti-TNF users vs. 1.7/1,000 in non-aTNF, for a hazard risk of 1.6. More than half the patients who developed OIs did so in the first 6 months after initiating
therapy. Baseline steroid use was an independent risk factors with a HR of 2.5. Interestingly, within the rheumatoid arthritis cohort, infliximab use was associated with a higher risk of OIs than etanercept (HR 2.9). The risk of tuberculosis was extremely low (0.1/1000 PY in non-aTNF v. 0.4/1000 PY among aTNF users). The second paper presented a meta-analysis of randomized clinical trials restricted to IBD. The authors identified 22 induction and/or maintenance RCTs evaluating aTNF vs. “standard” therapy. All OIs (bacterial, fungal, viral) were included. There were 9/1,000 OIs among aTNF users v. 3/1,000 among non-users for a HR of 2.0. The “number needed to harm” NNH was 500. Only one OI resulted in death (disseminated tuberculosis in a patient receiving golimumab in PURSUIT) for a rate of 1/4,000 patients treated. The most common OIs in this study were tuberculosis (2/1000), herpes simplex and oral and esophageal candidiasis. Varicella-zoster, CMV and Nocardia were less uncommon. Again, the relative risk of an opportunistic infection was higher in the first 8 weeks of therapy although this was not statistically significant. There were no differences among individual aTNF agents. It is worth mentioning that virtually all cases of tuberculosis developed in trials who screened for this disease at enrollment.

Comments: Although the risk of opportunistic infections appears to be twice as high among aTNF users, the good news from both studies is that the frequency of these infections is very low, between 3 and 9/1,000 patients treated. In IBD at least, considering a number needed to treat for benefit of around 5 and a number needed to harm of 500, the net NNT is 1:100 (for every patient likely to experience an OI, 100 patients will improve or go into remission). The reason for the different nature of infections in these studies is somewhat unclear. In the first paper, the investigators purposefully dismissed viral infections (more difficult to extract using ICD-9 codes) and candida (generally mild and relatively inconsequential). Yet, the high frequency of pneumocystis is puzzling. I suspect most of these cases derive from the Kaiser population in CA which may have a different composition and risk factors than the typical US population. Some infections may have been missed or under-reported. Particularly in the first study the definition of outcomes (infections) was very strict and a sensitivity analysis (using more relaxed disease codes) was not performed. Of particular importance in this case are Histoplasma and Coccidiomycosis which together comprise a great chunk of OIs in aTNF users throughout most of the Midwest and Southern US. The other factor to be kept in mind is that the patient populations in these two studies are markedly different, with a large contingent of RA patients in the first study and only IBD patients in the second (average age difference of 20 years!). Since a high proportion of patients with both RA and IBD received combination therapy it is difficult to tease out the effect of aTNF particularly in the second study. Finally, the second paper suffers from a wide variability of follow-up (short induction trials and lengthier maintenance trials) so a true incidence could not be calculated. Importantly, in the population-based study, steroids appear to be a very significant risk factor (if not the most important one) for OIs similar to what was seen in the TREAT registry (Lichtenstein et al). Thus, both papers provide a foundation for clinicians to address the balance of risks and benefits with their
patients prior to initiating biologic therapy. Furthermore, utilizing steroid-sparing therapies appears to be a very important goal in regards to safety in the management of IBD patients.


**In other news:**

4. **Fecal microbial transplantation not effective for UC in small trial.**

A series of 5 patients with refractory UC (including biologics) received open label “dual” FMT via NGT and enema. Only one patient had a partial response and some patients got clinically worse. All patients had an increase in CRP and some had fever. The composition of microbiota in the FMT recipients shifted towards the donor composition but this was quite variable and transient in nature. Interestingly in 3 of 5 patients the calprotectin levels dropped following FMT. I am sure that skeptics and optimists will interpret this data in different ways. What is clear is that an intervention that is essentially a “slam dunk” for C Diff carries completely different implications in IBD. The game is not over but the strategy needs to be changed given the complex relationships existing between the host immune system and gut microflora in IBD. Just as one dose of prednisone is not expected to substantially alter the immune system, short-term manipulation of the intestinal flora may not be enough to steer the microbial environment enough to cause a positive change. Stay tuned, this story is definitely not over.