1. Combination vs. biologic monotherapy in IBD

The issue of using anti-TNF biologics as monotherapy vs. in combination with an IMM such as azathioprine or methotrexate has been a subject of intense debate essentially since the approval of the first such drug 15 years ago. The data in rheumatoid arthritis is very strong in favor of combination therapy but, until recently, no good quality trials were published supporting this regimen in patients with IBD. The authors of this paper have performed a systematic review complete with summary recommendations and a practice algorithm regarding the use of anti-TNF biologics in patients with IBD. They reviewed data from multiple randomized and observational studies regarding biologic therapy with focus on efficacy, pharmacokinetics and main safety aspects. They point out that clear evidence of benefit from combination therapy exists only for IFX and Aza in patients with both Crohn’s and UC (SONIC and UC SUCCESS), but no direct evidence of benefit exists for methotrexate Mtx. This is, in large part owing to limitations of the design and methodology of the COMMIT trial (Feagan et al. – Gastro ’14). Pharmacokinetic data however clearly shows higher drug trough levels in patients receiving either Aza or Mtx and therefore the authors speculate that IFX in combination with Mtx may also be superior to monotherapy. Acknowledging that there are no direct comparative trials of adalimumab and certolizumab as mono- vs. combination therapy, the authors point out that pharmacokinetic data from RCTs may suggest that the advantages of combo therapy apply to all anti-TNF drugs regardless of their degree of “human-ness”. In the end, all these drugs are large foreign proteins (immunoglobulins) as humans do not spontaneously make anti-TNF antibodies. As far as adverse events, data from RCTs suggest that the risk of serious infections and opportunistic infections is similar with combination and monotherapy, although some observational studies suggest a higher risk with combination therapy. Again, the authors emphasize that the most important risk factors for infections overall is steroid use as shown in multiple studies. Regarding lymphoma risk, the authors conclude that the incidence is so small that data from RCTs lacks power and data from observational studies is likely subject to referral bias. However, a consistent signal is that combination therapy carries a higher risk of non-Hodgkin’s lymphoma compared to biologic monotherapy and similar to thiopurines monotherapy, suggesting that the lymphoma risk is primarily associated with the latter. This is also supported by another recent meta-analysis (see Kotylar et al. below). Also, both serious infections as well as lymphoma are more common in the elderly. In as far as hepato-splenic T-cell lymphoma a very rare but lethal form of lymphoma, the risk appears to be associated with duration of exposure, age (<35), gender (male) and mostly thiopurines therapy. Regarding the comparison between Aza and Mtx as combination agent, data from RCTs suggests that only Aza has a benefit in terms of efficacy while Mtx has only circumstantial, indirect evidence (by
increasing trough levels). There is no difference between the two drugs regarding serious infections but Mtx appears to be safer in terms of lymphoma risk although the data is scarce in IBD.

In contrast, adult rheumatoid arthritis data show that Mtx may be associated with an increased risk of lymphoma but adding an anti-TNF agent to Mtx does not appear to further increase the risk. From a practical prospective, the authors have developed an online tool available at www.BRIDGeIBD.com/therapy that can output a rating of appropriate, inappropriate or uncertain with regards to the use of combination therapy based on a number of clinical variables. In general, the consensus panel agrees that combination therapy appears appropriate for all Crohn’s disease and UC patients with extensive disease while monotherapy is appropriate for young males with limited disease. The duration of combination therapy is also discussed in brief. The risk-benefit ratio favors discontinuing the IMM particularly in young males who achieve deep remission whereas discontinuing the biologic is favored in elderly who have a higher risk of infections. Although the risk of flare after de-escalating to IMM is higher, re-introduction of the previous biologic is successful and safe in the vast majority of patients. On the other hand, the risk of lymphoma particularly in setting of thiopurine therapy is higher in the elderly.

**Comments:** this is a comprehensive review of the data on combination therapy which is an excellent resource for all gastroenterologists. In addition, the algorithm provided in the paper, as well as the online scoring tool are useful guidelines that can be used to facilitate clinical decisions. In the end, as it is often the case, the decision to use combination therapy with a biologic and IMM has to be individualized taking into account disease variables and patient preferences. As new biologics and small molecules enter the therapeutic arena in IBD, this practice paradigm is likely to change substantially in the future.


**2. Risk of lymphoma in IBD patients on thiopurine therapy**

It has long been known that the use of thiouropurines is associated with an increased risk of lymphoma, however data from population- and referral center-based studies are conflicting. Kotylar et al performed a meta-analysis with the primary objective to estimate the risk of lymphoma in thiopurine users and identify predictors of risk. Pooling data from 18 studies, the authors found an overall relative risk of lymphoma (measured as SIR) of 4.5 with wide differences between referral centers (SIR 9.16) and population-based studies (SIR 2.4). There was significant heterogeneity even among studies of similar origin (referral or population-based). The majority of lymphomas related to thiopurine use in IBD were EBV positive, occurred after more than 1 year of use and a disproportionate percentage originated in the gut (33%).
There was a significant difference between current users (SIR 5.7) and former users (SIR 1.4). Males had twice the risk compared to females. As far as the age interaction, while the relative risk was higher in young patients (<30) the absolute risk was higher in the older age group due to a higher background incidence of lymphoma in this elderly. Thus the number needed to harm decreased from 6,897 in those < 30 to 513 in those over 70. Although only limited data exists, the authors estimate that the risk of the severe hepatosplenic T-cell lymphoma is less than 1:20,000 person-years, higher in young males.

Comments: this study supports the idea that thiopurine use is associated with an increased risk of lymphoma and it also identified several potential risk factors including age, gender and duration of exposure. It is tempting to speculate in regards to the difference between referral and population-based studies. Patients in the former tend to be sicker, with multiple comorbidities, and subject to surveillance bias, but on the other hand, individual data from these case-controls studies is more accurate (including the dose and duration of treatment). In contrast, population-based studies provide a risk rate that is closer to the “real world” risk of lymphoma at the expense of lower accuracy regarding diagnosis, drug dose and duration. So the reality is likely somewhere in the middle. Given that the efficacy of these drugs has been questioned in some recent studies, this information seems to shift the balance between benefits and risks even further. I still think thiopurines are effective for some patients with steroid-dependent disease but the risks should be clearly discussed with the patient and the response objectively evaluated in cases where long-term use is planned. Older patients can’t seem to be able to win as the risk of serious adverse events with immunosuppressive therapy is highest in this age group whether thiopurines or biologics are used. (Source: Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of Lymphoma in Patients With Inflammatory Bowel Disease Treated With Azathioprine and 6-Mercaptopurine: A Meta-analysis. Clin Gastroenterol Hepatol. 2014 May 28. [Epub ahead of print].)

3. TNF-alpha antagonists do not increase the risk of cancer in IBD

Anti-TNF-α drugs have been associated with an increased risk of certain cancers, particularly lymphoma, melanoma and squamous skin cancer. However, this data is derived from studies with important confounders such as co-therapy with immunomodulators. Investigators in this study evaluated the risk of cancer associated with anti-TNF-α drugs from the nationwide patient registry in Denmark. This cohort included 56,146 adult patients with a diagnosis of IBD established from 1999-2012 of whom 4,553 (8.1%) were exposed to TNF-α drugs. Cancer cases were identified from the Danish Cancer Registry. Over a median follow-up of 3.7 years, 1.8% of patients exposed to TNF-α blockers developed a malignancy for an adjusted RR of 1.07. No site-specific cancers were found to be significantly in excess and there was no relationship of treatment duration with the risk of cancer. Although there was a trend for an increased risk of certain cancers such as skin, digestive and urinary tract, this was reversed after adjusting for
azathioprine use suggesting that the latter was the more important predictor. The authors estimate that their results could rule out a more than 36% relative increase in the risk of overall cancer over a median follow-up of 3.7 years among patients exposed to anti-TNF drugs.

**Comments:** The results of this study are reassuring in regards to the risk of cancer associated with anti-TNF drugs. In addition, it provides an estimation using population-based rather than referral center-based data. As in previous studies, the data seems to point towards an increased risk of cancer associated with azathioprine. There are some concerns regarding the validity of this data, however, and in particular related to the comparison group of biologic non-exposed IBD patients. First off, the prevalence of IBD in patients older than 15 in Denmark seems to be very high (1.2%). The high-average estimates in the US and Western World are 0.4%. Even if we “dilute” this cohort with younger Danish patients (< 15) it is unlikely that this will have a major effect on the denominator. Furthermore, it is possible that several unaccounted for variables increased the risk of cancer in the non-exposed group. For instance, 8% of patients in this cohort have been previously diagnosed with cancer which is rather high for a young (mid-30s) patient population. The average age in the two groups is not reported as the authors adjusted for it; yet, this might have been very useful to anchor the results. Control patients not only may have been older but also sicker (twice as many were taking cardiac drugs and 3 times as many anticoagulants – the latter is rather counterintuitive). Finally, the risk of lymphoma in the non-exposed group is also very high (0.55%) although only 16% used azathioprine. The corresponding rate in the US is around 0.16% or lower given the young age group (30-40). All these factors may have spuriously increased the risk of cancer, including lymphoma, in the non-exposed group and, in turn, decreased the relative risk among anti-TNF users. Finally, the authors admit that, due to the small number of cancer cases they cannot exclude a more than 2-fold increase in the risk of skin cancer or lymphoma or a higher risk with prolonged anti-TNF use. Despite its limitations, this study can be used as a reasonably good framework for deciding risks-benefits of anti-TNF therapy until better data becomes available.