1. Effects of withdrawal of IMM or biologic agents from patients with IBD

The promotion of top-down treatment strategies in IBD resulted in a greater proportion of patients achieving sustained remission early in the disease course without an actual “fail-first” step. Thus, it has become increasingly enticing for both patients and providers to consider “step-down” or de-escalation paradigms for reasons of safety, cost, national policies or personal preference. This review examines the evidence of IMM drug reduction and/or withdrawal in patients with IBD from the perspective of 3 scenarios: de-escalating IMM monotherapy, de-escalating IMM from combination therapy and anti-TNF therapy in patients on either mono- or combo-therapy. After a systematic search and review process, the authors were able to select 69 studies (43 retrospective, 7 RCT and 16 prospective cohort studies) encompassing 4672 patients. Stopping IMM monotherapy after a period of remission was associated with relapse rates from 15% at 6 months up to 75% at 5 years, which were about twice the rates seen while continuing the drug (mostly azathioprine). Re-treatment with IMM after loss of response was associated with success rates of 75-96% in both UC and Crohn’s disease. Reducing the dose or discontinuing IMM in patients on anti-TNF combo therapy had no effect on maintenance of remission rates; however, the overall relapse rates at 2 years in patients on combo therapy, de-escalated or not, were high at 55-60%. In addition, 50% of patients who discontinued anti-TNF drugs while in remission experienced a relapse at 2 years and this proportion continued to increase with time. Subclinical active disease (Hgb, CRP, WBC, calprotectin) and aggressive disease behavior were associated with an increased relapse risk. In most instances, retreatment with the same biologic was associated with regaining response/remission, although the role of interim treatment with IMM is unclear. Of the patients who discontinued anti-TNF drugs during the 2nd trimester of pregnancy, 10-15% experienced a flare by the end of the 3rd trimester and 15-30% a relapse post-partum. Most patients were able to regain disease control after reintroducing the biologic despite only a small minority being on IMM. The rate of infusion/injection reactions was low. The authors concluded that the decision to decrease or withdraw IMM therapy should be individualized in IBD patients based on the risk-benefit profile.

Comments: These results represent a departure from the classic dogma that “once on IMM or biologic – always on IMM or biologic”. Although the relapse rates appear to be high across all therapeutic classes, a substantial minority of patients appear to be able to use intermittent therapy or discontinue IS drugs altogether. The common denominator for successful cases seems to be deep remission (clinical, biological and endoscopic) at the time of drug withdrawal. Limitations of all these studies include; the retrospective nature, lack of standardization, selection bias and the short-term follow-up. Thus, the long-term impact of discontinuing or de-
escalating therapy in both UC and CD patients is unknown. Although, this data reopens the conversation about a previously maligned strategy which is “episodic” or “cyclical” therapy. At least with a-TNF and for patients with milder forms of disease and lower risk of progression, structural damage and complications. The higher risk of immunogenicity with biologics also has to be kept in mind, as further prospective studies are clearly needed. The decision-making diagrams provided with this paper (below) are also informative.


2. Risk factors for dysplasia progression in Ulcerative Colitis

Patients with colonic inflammation from both UC and CD are at increased risk of colon cancer, and patients diagnosed with dysplasia as part of UC surveillance are at further increased risk. Risk factors for the development of dysplasia include; sex, age, disease duration and extent, PSC and inflammation and are well described, but risk factors for dysplasia progression less so. This is, however, very important as it can affect the decision to continue surveillance or proceed to
colectomy. In this single-center retrospective review from one of the largest IBD programs in the UK, St. Mark’s Hospital in London, investigators analyzed outcomes of low-grade dysplasia (LGD) in a cohort of 172 patients with UC, selected from a surveillance program over a period of 2 decades and followed for a median of 4 years. The majority of patients were male, median age 60, with 23 years of disease history and essentially all had extensive UC. Overall, 33 patients (19%) developed high-grade dysplasia HGD or CRC, for an incidence rate of 4%/year (1.5% for HGD and 2.5% for CRC). Among the 21 patients with LGD who underwent colectomy immediately after diagnosis, histology revealed concurrent CRC in 33% and HGD in 14%. Only 38% of these patients were confirmed with LGD after surgery. A baseline diagnosis of non-polypoid dysplasia - HR 8.6, invisible dysplasia – HR 4.1, indefinite dysplasia – HR 2.8 and lesion size > 1 cm – HR 3.8 were significantly associated with the development of HGD and CRC, among patients with LGD at enrollment. Interestingly, neither a diagnosis of PSC, nor that of active inflammation panned out as risk factors in multi-variate analysis. Colonic stricture was an independent risk factor for colon cancer (HR 16.3) in univariate analysis, 4 of 6 patients with a stricture were eventually diagnosed with CRC. There was a significant positive correlation between the number of risk factors present and the cumulative risk of developing HGD and CRC. The 5 year risk of developing advanced neoplasia was 1.8% with no risk factors, 18% with 1 risk factor, 53% with 2 risk factors and a whopping 81% at 2 years with 3 risk factors (or 40%/year). Only 30% of CRC were preceded by HGD.

**Comments:** Despite its major limitations, this study identified 3 important risk factors for the development of advanced neoplasia among patients with UC and LGD diagnosed during surveillance: lesion shape (non-polypoid or invisible), size (> 1 cm) and indefinite histology. In addition, a colon stricture in patients with UC may also be considered a major risk factor, although the small sample size made the very high odds statistically not significant. As shown in multiple previous studies, small polypoid lesions were associated with a low cancer after endoscopic polypectomy, suggesting that these may be sporadic adenomas occurring within the area of colitis. There are multiple potential sources of bias which make generalization of this data difficult. There was a huge rate of concurrent CRC and LGD among patients who underwent immediate colectomy after LGD diagnosis. Having a very low number of biopsies/procedure (median 12), along with a high rate of CRC without preceding HGD (70%) strongly suggests a detection bias (high rate of missed lesions at colonoscopy). Interestingly, with the advent of chromoendoscopy (CE), dysplasia detection including non-polypoid dysplasia rate went up two-fold and “invisible” or “flat” dysplasia detection decreased in half. Although, high-definition endoscopy was not evaluated separately. A previous study from the same center also showed that the rate of “interval” cancers decreased by more than half with the advent of CE suggesting an important role for this technique in dysplasia surveillance. I suspect the reason neither PSC nor active inflammation panned out is because these are independent risk factors for LGD, and therefore may have washed out in the subset analysis.

3. Decreased mortality with surgery vs. medical therapy in older Medicare UC patients

UC can be treated medically or surgically. Given the high “cure” rate with colectomy, many factors including; quality of life, morbidity and mortality, drive the medical decision about surgical or medical therapy in these patients. Whether one has an advantage over the other is unclear. The authors of this retrospective cohort study analyzed data from a large administrative database (Medicare and Medicaid) covering 50 US states, over more than 10 years. Patients with “advanced” UC were identified based on pre-specified criteria (ICD-9 codes and medications). 830 patients who were identified as having “elective” surgery based on CPT codes were matched with 7,500 control patients who received medical therapy. The mortality rate associated with elective colectomy was lower than that associated with medical treatment (3.4% vs. 5.4% per year), HR for death 0.7, although the effect was limited to those aged > 50. Patients with more comorbidities and those using steroids had higher mortality risk regardless of treatment group. Patients pursuing colectomy were more likely to develop infections and use narcotics, and less likely to use steroids compared to the medical group.

Comments: Although this study showed a potential benefit of elective surgery over medical therapy in older patients with UC, it is unclear if these results can be extrapolated to other patient populations. The study cohort was fairly heterogeneous and not necessarily representative of the US population, encompassing adults > 65 or younger patients on disability (i.e. Medicare or Medicaid). It is virtually impossible to control for disease severity, although arguably, most patients who had “elective” surgery may have failed medical therapy and only a minority of patients in any population-based study are expected to have surgery for neoplasia. However, a very small fraction (<20%) of these patients were treated with immunomodulatory therapy and < 10% received biologics, which is hardly reflective of moderate-severe UC in the general population. The cause of death was also not examined, although it could provide further insight on the difference in outcomes between the two groups and may represent the most important argument, which is if this data should be taken into consideration when educating patients about their options. The interesting finding is that steroids seem to increase the risk of death regardless of the medical or surgical approach, which is something that has been described in multiple previous studies. While association does not mean causality, this study confirms that prolonged steroid use is a marker of increased risk of complications including death in UC. This is clearly something that should be emphasized in conversations with patients when weighing risks and benefits of therapy.