1. The REACT trial puts a negative spin on combination therapy in Crohn’s

Step-up therapy may be appropriate for some patients with moderately active Crohn’s disease but top down therapy has been advocated in patients with severe disease based on a small number of prospective trials. It involves using combination therapy with an anti-TNF biologic and an immunomodulator - usually thiopurine. REACT was an open-label cluster randomized controlled trial in which community practices -and not patients- were randomized to either early combined immunosuppression (ECI) or conventional management (CM). Providers in the ECI practices were provided with an algorithm involving an induction course of steroids followed by combination therapy with adalimumab + IMM. Providers in the CM group were allowed to manage patients based on their standard algorithm. The primary outcome was the proportion of patients in steroid-free remission (HBI score <4) at 12 months. A total of 1980 patients were randomized (21 ECI practices and 18 CM practices). At baseline, more than half the patients were already in remission and more than 30% of them were already receiving anti-TNF therapy -including 12% on combination therapy. A slightly higher number of patients in ECI practices than CM practices were receiving combination therapy at both 12 and 24 months, however the proportion of patients on combination therapy was <10% higher compared to the baseline. There was no difference between the ECI and CM groups for the primary outcome (steroid-free remission) although there was a small reduction in the risk of surgery (3%) and serious disease-related complications (6%). The difference in hospital admissions was not significant, and there was no difference in serious drug-related adverse events between the 2 groups.

Comments: Although the results of REACT are disappointing, this trial suffers from major methodological limitations. The majority of patients were in remission at baseline which is hardly a good place to start a trial of top-down vs. step-up therapy. In addition, a significant minority (30%) of patients were already on anti-TNF drugs, alone or in combination with IMM and no objective markers of disease activity were collected (either CRP, calprotectin or endoscopy). Thus, it is no surprise that the investigators have set themselves up for failure. One has to note that the REACT trial was different in its patient selection from both the “Top-down” trial by D’Haens et al. (Lancet ’08) and the SONIC trial (Colombel – NEJM ’10), which enrolled patients with moderate-severely active disease at baseline. Therefore, the results of REACT cannot be extrapolated to most clinical practice scenarios. A follow-up REACT2 trial apparently plans to use objective parameters (endoscopy) to assess disease activity following a similar treatment algorithm.

2. Predictors of Crohn’s disease in IBD-U patients following colectomy with IPAA

Restorative proctocolectomy with IPAA is the surgical procedure of choice in patients with UC refractory to medical therapy or complicated by dysplasia. Recently, several surgical centers of expertise have advocated the use of IPAA even for patients with IBDU -aka indeterminate colitis- based on positive experience in small series of patients. In this single-center, single-surgeon study, investigators sought to determine the risk factors for CD development following colectomy with IPAA in a series of patients with IBDU. Of the 551 patients who underwent this surgery, 177 (32%) were preoperatively classified as IBDU based on atypical disease distribution (skip lesions), small bowel involvement, perianal disease or granulomas on biopsy. The median disease duration at the time of the surgery was 5 years and the majority of patients were non-smokers and had pancolitis, but only 5% had PSC. The indication was refractory disease in 87% and neoplasia in the remaining 13%. After a median of 37 months from the ileostomy closure, 22% of patients developed Crohn’s disease of the pouch or neoterminal ileum. The only predictor for CD in these patients was younger age at disease onset. For each year of life younger at diagnosis, the risk of CD increased by 4%. However, there was no information on IBD serologies, smoking habits after surgery, or the use of medications before and after the operation. The authors speculate that there are differences in the immune system dysregulation in patients with earlier disease onset that predispose them to develop Crohn’s disease following IPAA surgery.

Comments: Identifying risk factors for CD of the pouch is essential given the high rate of pouch failure in these patients (up to 45%). Although young age at diagnosis is a plausible risk factor, the results may well be the product of a type I error. Even if the association with age was highly significant, there were more than 20 candidate variables analyzed with only 33 patients being diagnosed with CD. Thus, the association described here may have occurred purely by chance. Further studies in this important area are clearly needed before definitive conclusions can be drawn.