Inflammatory Bowel Disease Seattle Journal Club

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1. Ileal pouch-anal anastomosis (IPAA) and the risk of cancer in UC patients

Proctocolectomy with stapled IPAA has become the surgical technique of choice in UC patients with refractory disease or diagnosed with neoplasia as it has superior functional outcomes compared with the handsewn technique; however the latter also allowed the performance of mucosectomy of the rectal cuff which was thought to be safer in patients with pre-existent neoplasia especially of the rectum. The long-term risk of neoplasia of the anal transition zone (ATZ) (rectal cuff) following stapled IPAA surgery is unknown. In this retrospective series, investigators determined the long-term risk of dysplasia and cancer developing in the ATZ of patients who underwent proctocolectomy for UC at a single tertiary care center. A total of 285 patients who underwent surveillance endoscopy every 1-2 years were selected from a large cohort of patients with IPAA. Only 13% of patients underwent colectomy for neoplasia. During a median post-operative follow-up of 15.4 years (0.6-26), no patients developed adenocarcinoma and dysplasia was diagnosed in 9 (6 LGD and 3 HGD), all within the first 10 years after surgery. The 10 and 15 year rate of dysplasia was estimated at 2.9% and 3.4% respectively. Pre-operative diagnosis of dysplasia or cancer was associated with a HR of 6.4 of developing neoplasia at the ATZ. Of the 9 patients who developed dysplasia, 4 underwent mucosectomy with IPAA advancement and remained free of dysplasia at follow-up. In the other 5, low- or high-grade dysplasia was only sporadically diagnosed during surveillance with subsequent biopsies showing no dysplasia.

Comments: Although the results of this study are reassuring there are a number of major limitations that affect the validity of the study. First off, this is a selected cohort (54% of those in the database) of patients who underwent IPAA at a single institution. The surveillance dropout was substantial particularly after 10 years. It is also difficult to find a plausible explanation for the resolution of both LGD and HGD in patients who were diagnosed as such during surveillance. Nevertheless, it appears that the risk of cancer in patients with stapled IPAA is very small, at least in patients who have no pre-operative neoplasia. Since the functional outcomes of stapled IPAA is superior to that of handsewn pouches, this study supports the idea of preferentially performing stapled anastomoses in virtually all patients with refractory UC with the exception of those who have rectal cancer within 10 cm of the anus.

**2. Laquinimod for treatment of Crohn’s disease**

Current medications are only moderately effective for Crohn’s disease, and the best drugs available are costly, associated with frequent loss of response and need to be given parenterally. Laquinimod is a novel oral agent that has a NF-kB-mediate inhibitory effect on dendritic and T-cells and is being developed for treatment of multiple immune- and non-immune mediated conditions including multiple sclerosis, Huntington’s disease and lupus nephritis. In this phase 2-a placebo-controlled randomized study, investigators assessed the safety and efficacy of escalating doses of LQ in patients with moderately active CD who failed other therapies including biologics. A total of 180 patients were randomized to receive placebo or escalating doses of LQ from 0.5 mg to 2.0 mg in sequential cohorts. It is unclear if patients were eligible to participate multiple times in different phases of this sequence (either drug or placebo). The study groups were slightly imbalanced in that patients in the placebo and low-dose groups had higher CRP and fecal calprotectin compared to the higher dose groups. Overall side-effects were not different between LQ and placebo, but more patients dropped out in the higher-dose groups due to severe adverse effects. The most common side-effects with LQ were headache, abdominal pain and elevated amylase. At week 8, the proportion of patients with response or remission was higher in the 0.5 mg LQ group compared to placebo (55% vs. 32% and 48% vs. 16%, respectively), but higher doses showed no benefit. No consistent effect on the CRP or calprotectin was seen with the exception of low-dose LQ which was associated with a higher normalization of CRP compared to placebo.

**Comments:** The interpretation of the laquinimod efficacy data is difficult due to a significant “divergence” in the randomization process: patients with more active disease received a lower dose of medication compared to those with less severe disease. The authors also point out in their discussion that this phase-2 study was exploratory and not powered for efficacy. However, a “divergent” dose-effect relationship, as in the movie by the same name, does not bode well for drugs in development (see the story of tofacitinib in Crohn’s). Although the sponsors are planning a phase 3 study, the potential benefit of laquinimod for CD is difficult to predict at this point. The major appeal of this drug is the oral bioavailability and the relative safety at low doses.


**3. Mesalamine dose optimization in minimally active ulcerative colitis (the DEAR study)**

Mucosal healing is an important goal of therapy in UC as it associated with lower risk of flares, hospitalizations and surgery. However endoscopy is invasive and expensive and therefore surrogate biomarkers of disease activity such as calprotectin have great appeal for disease monitoring. The authors of this study have performed an open label randomized control trial to determine if high-dose mesalamine is effective for patients with UC in symptomatic remission but with an elevated FC. To be eligible, subjects had to be on < 3 g mesalamine daily, have an elevated FC, have had > 1 flare in the previous 2 years and not be on biologic therapy. A total of 52 patients were randomized to continue standard (2.4 g/day) or high-dose (4.8 g/day)
mesalamine MMX in an open label fashion. Topical therapy was discontinued. A group of UC patients in remission with normal FC was used as a non-interventional control. The primary outcome was the proportion of patients in clinical remission and with a FC < 50, 6 weeks after treatment. This was achieved by 27% of patients in the dose escalation group and 3.8% of patients in the standard dose group. Time to clinical relapse was shorter in subjects with FC > 200 vs those with FC < 200 at the completion of the study. No adverse events were seen in either dose group.

**Comments:** Several important observations are noteworthy in this study. First, even if the endoscopic disease activity was not assessed, about half of the UC patients in symptomatic remission had evidence of disease activity when evaluated using objective biomarkers. Second, although there is a significant benefit from maximizing the dose of 5-ASA in some patients, there appears to be a ceiling effect as, even at high dose, 15-20% of patients had a calprotectin > 200, implying that there is a subgroup of patients in apparent remission who won’t achieve mucosal healing regardless of the dose of 5-ASA. There are several limitations to the present study: relatively small size, lack of blinding, inclusion of a significant proportion of patients with proctitis in which oral mesalamine is less likely to be effective and FC less likely to be reliable, and lack of endoscopic assessment. However this study shows fairly clearly that “treatment to target” or treatment optimization based on objective parameters in UC patients appears to be effective. Also, FC monitoring should be considered in patients with short remission duration (< 1 year) to document the existence of persistently active disease which may increase the risk of flares. It would be interesting to determine if the same principle of treatment optimization also applies to UC patients who are in clinical remission on biologics or thiopurines but have persistently active endoscopic disease. A larger RCT study will likely follow based on this preliminary observation.