1. Comparative efficacy of medications for post-operative prevention in Crohn's disease

The risk of surgery in patients with moderate-severe CD is substantial and post-operative recurrence is the norm. Endoscopic recurrence at 1 year exceeds 70% and clinical recurrence at 5 years is over 50%. Furthermore, a substantial proportion of patients with CD will require multiple surgeries during their life-time resulting in additional functional and metabolic complications. Medical treatment for post-operative prevention in CD has been the subject of multiple studies but comparative data is lacking. In this paper, investigators are reporting on a systematic review and meta-analysis of RCTs evaluating the efficacy of pharmacological interventions for post-operative prevention. A total of 21 RCT studies comprising 2006 subjects met the eligibility criteria. The criteria for clinical and endoscopic recurrence were relatively homogeneous. For clinical and endoscopic recurrence, antibiotics (RR 0.26, 0.41), immunomodulators (RR 0.36, 0.33), IMM + antibiotics (RR 0.11, 0.16) and anti-TNF drugs (RR 0.04, 0.01) were significantly more effective than placebo. Mesalamine was slightly more effective than placebo for clinical but not endoscopic recurrence and budesonide was ineffective for either. Based on indirect comparisons, the authors concluded that anti-TNF monotherapy was superior to all other strategies in decreasing the risk of clinical and endoscopic recurrence with large effect size estimates. Combination IMM + antibiotics was not significantly different from IMM or antibiotics alone.

Comments: This paper does a nice job summarizing the relatively scarce data on the efficacy of medical therapy for post-operative prevention in CD. The results support the idea that antibiotics, IMM and anti-TNF therapy are effective whereas mesalamine and steroids have no preventive benefit. Furthermore, as expected, anti-TNF drugs seem to be the most effective agents in this regard. However, before drawing hard conclusions, one has to acknowledge the limitations of this meta-analysis. There is a relatively small number of studies that have performed head-to-head evaluations between agents and therefore the indirect comparative data is not very robust. Furthermore, this meta-analysis makes the assumption that patients enrolled in these studies were homogeneous which is not necessarily true. There may be important confounders such as smoking, disease location (small bowel, colon), behavior (stricturing vs. penetrating), number of previous surgeries, previous therapies, drug dose, etc. that may significantly affect the results. That said, further larger prospective studies (such as the recently concluded PREVENT study) are likely to confirm these findings.


2. Should we treat CMV in patients with IBD flares?

There is quite a bit of controversy regarding the benefit of antiviral therapy in patients with IBD who have evidence of CMV infection on tissue biopsies. Some retrospective series showed benefit whereas prospective studies showed no value of antiviral therapy. In this study, investigators have performed a nested case-control study in over 1,100 patients with IBD who had colon biopsies evaluated for CMV over a period of 7 years. Biopsies were arbitrarily classified as high or low CMV density based on the presence of 5 or more...
macrophages with intra-nuclear inclusions. CMV-negative patients were used as controls. Overall, 6% of patients were found to harbor CMV in colon biopsies and follow-up was available for 50 patients (16 high-grade and 34 low-grade). All high-grade patients were treated with ganciclovir or valganciclovir, whereas only 20 low-grade CMV patients received anti-viral therapy. Patients with high-grade CMV were less likely to be treated with steroids or anti-TNF drugs at baseline (before CMV diagnosis). Although CMV + patients had higher ESR and CRP compared to IBD controls, there was no difference in the surgery-free survival at 1 year. Among low-grade patients, antiviral therapy decreased the risk of surgery (HR 0.39). High-grade patients (all receiving antiviral drugs) fared the best with a trend towards lower surgery rates compared to CMV-negative controls. Patients with low-grade CMV who did not receive antiviral therapy were nearly 5 times more likely to have surgery within 1 year than patients with high-grade disease.

Comments: This study suggests that anti-viral therapy may benefit patients with CMV inclusions in colon biopsies regardless of viral load. However, there are several caveats. The inclusion criteria were not defined as CMV testing was based purely on the clinician’s judgment. The number of cases is small and if the authors included the four CMV + patients who had colectomy within a week of starting antiviral therapy (retrospective intent to treat), the differences would no longer be significant. It is unclear why the authors chose 5 inclusions as their cut-off but it is interesting to note that all patients with > 5 inclusions were treated with anti-viral therapy. There is no information on testing and/or treatment for C Difficile. Finally, the most important question not answered by this study is what happened to the immunosuppressive therapy once the diagnosis of CMV was made. Some studies suggest that decreasing the immunosuppression (particularly the steroids) was beneficial in CMV+ patients whereas others showed no effect of adjusting the immunosuppression and particularly the biologic. Thus, the CMV controversy continues although, considering the safety and low cost of anti-viral therapy, it is probably reasonable to treat patients who have evidence of CMV disease based on high-density biopsies and high titer CMV DNA and/or other systemic manifestations.


3. Long-term outcomes of thalidomide in refractory Crohn’s disease

Open-label and retrospective studies have suggested that thalidomide is beneficial in patients with refractory Crohn’s disease. Although the mechanism of action is unknown, an anti-TNF effect was described in vitro. In this retrospective uncontrolled series, the authors report a single center, long-term experience with thalidomide for patients with refractory Crohn’s disease. Thirty-seven adult patients with refractory CD were treated with thalidomide at doses between 50-200 mg daily. The vast majority had failed anti-TNF drugs, immunomodulators and were steroid-dependent or refractory. Almost 75% had previous surgery. In patients who were able to continue thalidomide for a median of 4.4 months, the response and remission rates at 1 year were 54% and 11% respectively and were dose-dependent. The response lasted about 5 months and eventually about half the patients relapsed although there were a few long-term responders. 40% of patients were able to discontinue steroids. Interestingly, although there was a drop in ESR, the CRP did not change with therapy. 16 patients (43%) required surgery at 2 years, and there was no significant difference in the need for surgery among responders vs. non-responders. Two thirds of patients experienced side-effects and half of them stopped the drug. Neuropathy (38%) was the most common side-effect and 3 patients (20% of those who developed neuropathy) had irreversible symptoms. No patients experienced a thromboembolic event or a serious infection in this series.

Comments: Although the authors conclude that thalidomide appears safe and effective for patients with refractory Crohn’s disease, the overall long-term response rates were small and there was no difference in the rate of surgery between groups. The assessment of response was subjective and the reason for the lack of
improvement in CRP is unclear. Side-effects were quite common although most resolved after withdrawal. However, 3 patients experienced irreversible neuropathy. The monthly cost of this drug is substantial and exceeds that of biologic therapy although the authors state that all prescriptions were covered by insurance. The mechanism of action of thalidomide is unclear but presumed to be mediated via TNF-alpha although lenalidomide, a more potent analogue of thalidomide with anti-TNF properties, showed no benefit in moderate-severe CD.