1. Budesonide MMX for Mild-Moderate Ulcerative Colitis: the CORE I and II Studies

Budesonide is a gut-specific steroid owing to extensive first-pass metabolism in the liver. Budesonide MMX (B-MMX) is a once-daily formulation that achieves both delayed (pH-dependent) and extended release of the drug throughout the colon by using a multi-matrix system technology (MMX). Investigators now compared budesonide MMX with placebo and mesalamine 2.4 g in patients with mild to moderate UC enrolled in a randomized multicenter trial. The primary end-point was remission at week 8 using the UCDAI score (clinical and endoscopic). Patients with proctitis were excluded and patients on 5-ASA at the screening visit were required to wash out. A total of 489 patients were randomized to B-MMX 9 mg, 6 mg, mesalamine 2.4 g or placebo. Approximately 60% of patients had previously used and/or failed mesalamine. Patients receiving B-MMX 9 mg had a modest but significantly higher rate of remission compared with placebo, 17.9% vs. 7.4%, whereas the 6 mg dose and the mesalamine group were non-significantly higher than placebo. No significant difference was found in patients with extensive colitis between any of the treatment groups and placebo. The study was also underpowered based on pre-enrollment estimates although in a positive study this may be less relevant. In a separate but similar study (CORE II), budesonide-MMX 9 mg once daily was also superior to placebo (17.4% vs. 4.5%). However, it was not significantly better than budesonide EC (controlled, ileal release without MMX) which had a remission rate of 12.6%.

Comments: Together, these two studies demonstrate that budesonide-MMX is effective for patients with mild-to-moderately active ulcerative colitis. A few other observations are worth mentioning: the introduction of mucosal healing as a clinical trial end-point has drastically reduced the response and remission rates that we got accustomed to in previous IBD trials. This was also evident in another recent trial using adalimumab for UC. Although it has been approved by the FDA, it is unclear what place will budesonide-MMX take in the UC treatment algorithm. Although the study was not powered to detect a difference, B-MMX was not superior to 5-ASA (or budesonide EC in CORE 2) despite the fact that the majority of patients were 5-ASA failures. It is therefore uncertain how the drug would compare with mesalamine in patients who are 5-ASA naïve. Furthermore, since the drug is only approved for induction it is unclear if the safety benefit of B-MMX would stand the cost trade-off with prednisone under the same circumstances. Prednisone has been previously shown to be superior to budesonide for treatment of ileal-R sided Crohn’s disease (Otley and Steinhart – Cochrane Database Syst Rev ’05).


2. Safety and Effectiveness of Long-term Allopurinol-Thiopurine in IBD.

Almost 50% of patients treated with thiopurines (azathioprine, 6-MP) discontinue therapy due to lack of efficacy, adverse events or both. The metabolic pathway for thiopurines has been well described. Overall there is a trade-off between the active metabolite believed to be 6-TGN and several side-products, of which 6-MMP (driven by the TPMT enzyme) is thought to be hepatotoxic. Small series have shown that a combination of allopurinol—thiopurine may be effective in patients who achieve very high levels of 6-MMP and low levels of 6-TGN (also called hypermethylators). The mechanism of action of allopurinol in this combination is unknown. In this retrospective case series, the authors are reviewing their experience with 77 patients with IBD who were treated with this combination at two large referral centers over a period of 7 years. All patients failed or were intolerant to thiopurine monotherapy. After the addition of 100 mg allopurinol, the dose of Aza or 6-MP was decreased to 25-30% of the original dose and then the dose was adjusted based on the clinical, biological or metabolic (6-TGN) response. Seven patients were also receiving anti-TNF therapy and 23% were on steroids. The median doses of 6-MP and Aza during combination therapy was 0.39 mg/kg and 0.64 mg/kg respectively. During combination therapy, there was a significant increase in 6-TGN levels and a marked drop in 6-MMP, with a corresponding drop in the 6-MMP/6-TGN ratio from 68 during monotherapy to 1.3 during combination therapy. 21% of patients had to discontinue combination therapy due to adverse events, lack of efficacy or patient’s preference and 25% had dose-limiting adverse events including transient mucosuppression in 12 patients who were able to continue therapy after dose adjustment. No serious infections were reported in this cohort. At 60 months, 65% of patients were still on combination therapy and the rate of steroid-free remission increased from 44% to 61%. One patient was able to discontinue anti-TNF therapy. Interestingly, 32% of patients who were considered “hypermethylators” by 6-MMP levels had “intermediate” TPMT enzyme activity. In addition, 19% of patients on combination therapy had persistently elevated liver tests despite a marked decrease in 6-MMP, indicating that both TPMT phenotype and thiopurine metabolites may not be perfect surrogate markers for safety.

Comments: This is the largest series reported on combination therapy with thiopurine-allopurinol. Most gastroenterologists continue to feel uncomfortable using this regimen due to the significant potential for side-effects and especially bone marrow suppression and would still choose either methotrexate or a biologic under these circumstances. This concern is further amplified by the current labeling for Aza and 6-MP which lists the combination with allopurinol as a contraindication. Although the efficacy data clearly requires further comparison studies, this paper at least provides a basic foundation for
those willing to venture down the crafty road of pharmacologic manipulation of thiopurines. In addition, this regimen may provide an alternative for patients who fail standard therapy including biologics. In my experience, the ideal candidates for this therapy are middle age patients who are very reliable and live in relative proximity to the office or medical center.


3. **Adenomas as Predictors for Advanced Neoplasia in IBD Patients**

Patients with UC and extensive Crohn’s colitis are at increased risk of neoplasia. Colitis-associated cancer is thought to be preceded by dysplasia which can be flat (invisible) or elevated (polypoid). Dysplasia can be classified as low-grade or high-grade and resectable (ALM) or non-resectable (DALM). This study reports on the predictive value of adenomas on the subsequent development of advanced neoplasia (HGD or cancer) in IBD patients by comparing patients with IBD with adenomas, IBD without adenomas and non-IBD patients with adenomas. Patients were initially identified using a nationwide pathology database in Netherlands, but only patients evaluated in 7 academic medical centers were eligible for the study. Subsequent adenomas developed in 33% of IBD-adenoma, 12% of IBD-non-adenoma and 44% of non-IBD adenoma groups respectively. The 5-year cumulative incidence of advanced neoplasia (AN) was 11% in the IBD-adenoma group vs. 3% in the IBD-non-adenoma and 5% in the non-IBD adenoma groups respectively. Colon cancer developed in 6 patients in the IBD-adenoma group (3 preceded by HGD), 4 in the IBD-non-adenoma group (only 1 preceded by LGD) and 3 patients in the non-IBD adenoma group (obviously all preceded by dysplastic polyps). The authors conclude that there is an increased risk of advanced neoplasia in IBD patients with adenomas compared with non-adenoma IBD patients and non-IBD patients with adenomatous polyps.

**Comments:** This study is rather confusing owing to its retrospective nature, and I think the conclusions are overstated. Of the initial 2000 patients from the pathology database only 412 patients were selected and all these belonged to tertiary referral centers. Most excluded patients had missing data or were lost to follow-up. 20% to 40% of the original adenomas identified were only biopsied and not removed at the initial colonoscopy, and therefore the accuracy of the initial pathological diagnosis is unclear. Only about half the patients in each group underwent follow-up colonoscopies with “random” biopsies, the time interval and number of such “random” biopsies is unknown and the use of chromoendoscopy is not reported (presumably nil). Finally, the 2% rate of interval cancers in the screening population (non-IBD adenoma) is substantially higher than the one reported in similar series from the US or Europe (Winawer et al. – NEJM ’93, Kahi et al. – Clin Gastroenterol Hepatol ’09), again raising concerns of selection bias, among others. Some of the relatively high interval cancer rates may have to do with the available endoscopic technology at the time, although the National Polyp Study by Winawer et al.
was performed in large part using optical colonoscopy and still showed a very low interval cancer rate (0.6/1000 patient-years). In conclusion, I believe this study is an outlier among a majority of publications indicating that resectable (elevated) dysplasia has a favorable outcome in patients with IBD who undergo regular surveillance colonoscopy and this outcome is comparable with IBD patients without dysplasia. Also, the rate of colon cancer in population studies appears to be lower than originally estimated and high-definition chromoendoscopy is likely the best method for IBD surveillance.