1. **Add some spice to UC treatment using curcumin**

Curcumin is a naturally occurring phenol extracted from turmeric and has been used for centuries in ayurvedic and traditional Chinese medicine for its presumed anti-inflammatory properties. In vitro, curcumin can inhibit NF-κB-modulated pathways and can improve experimental colitis in animal models. It may also have anti-oxidant and anti-neoplastic properties when used in conjunction with other chemotherapeutics. In this pilot placebo-controlled trial the authors have randomized 50 mild-moderate UC patients who were active despite treatment with mesalamine to treatment with either curcumin 3 g/day or placebo for 1 month. Remission rates were significantly higher in patients receiving curcumin 53.8% vs. 0 with placebo (p=0.01). Clinical response (65.3% vs. 12.5%) and endoscopic remission (38% vs. 0) were also significantly higher in the curcumin group and there were no serious adverse events in either group.

**Comments:** There is a strong interest in the medical and naturopathic community for findings alternative treatment options for UC that are both safe and effective. The present small pilot trial adds to the meager body of evidence supporting curcumin as an additive agent for induction of remission in mild-moderate UC. However promising this might be, this study also checks several items in the “too good to be true” list. These include remarkable response and remission rates and particularly the “0” placebo clinical and endoscopic remission rates which are essentially unheard of. For similar disease severity, trials of budesonide MMX have shown response and remission rates of merely 10% over placebo. Therefore there are serious concerns about the risk of bias, unblinding or conflict of interest on the side of the investigators. Curcumin is a yellow pigment which can be easily detected in stool and urine and its particular odor can be detected in perspiration. The authors have not performed a dose-finding study and it is unclear how the study dose was determined. However, if these results can be replicated in a well-designed trial, curcumin, which is relatively cheap, could make its way as the first natural product to be part of the treatment algorithm for UC. Its place in therapy may be somewhere between 5-ASA and steroids if the current results hold true.


2. **Detectable infliximab in feces associated with lack of response to therapy in UC**

Lower IFX trough levels have been associated with loss of response to therapy in patients with IBD (secondary failure). The mechanism for primary non-response is unclear but a high inflammatory burden (CRP, serum TNF-alpha) or a drug sink (clearance) have been proposed as possible explanations. Clearance of monoclonal antibodies happens primarily through the reticulo-endothelial system but a new study suggests that loss of drug in feces may be an important mechanism. Investigators from a Dutch hospital analyzed fecal and serum IFX concentrations in 30 consecutive patients with severe UC during the first 2 weeks of therapy and the outcomes were evaluated up to 3 months. They were able to detect IFX in 66% of fecal samples with the highest concentrations in the first few days after infusion. Non-responders at 2 weeks had significantly higher fecal IFX concentrations compared to responders (5.01 μg/mL vs. 0.54 μg/mL) but no significant differences in fecal IFX concentrations were found.
between clinical responders and non-responders at 3 months and the presence or absence of endoscopic healing at week 8. Furthermore, there was no correlation between fecal and serum levels of IFX were seen. Patients with detectable IFX in feces had significantly more severe colitis, lower albumin levels and higher fecal calprotectin. The authors conclude that intestinal loss of anti-TNF biologic is associated with treatment failure in patients with severe UC.

Comments: This is the first study to demonstrate the loss of mAb drugs in the feces of patients with active UC. While this is quite intriguing, the results do not provide conclusive evidence that this phenomenon is anything but another marker of disease severity. In fact, the levels of IFX in serum and feces did not correlate and while there was some difference in stool IFX among responders and non-responders at week 2, no such difference was seen between more meaningful endpoints such as responses at weeks 8 and 12. It may just be that it is not the stool concentrations that matters but the actual amount of drug that is lost in the feces (i.e. concentration x volume) and the volume part was not measured. Furthermore, there was also no difference in early serum IFX levels between responders and non-responders. Taken together, this data indicates that fecal IFX levels are likely only a marker of disease severity and implicitly “leaky gut” rather than an important mechanism of drug clearance. It would be interesting to see if this data can be replicated with injectable biologics.


3. Forty-Year analysis of UC surveillance reveals benefits, uncertainties

The increased risk of CRC in patients with extensive UC is well established. However the relative risk has been a matter of debate as recent studies have shown a much lower rate of cancer compared to studies performed 2 decades ago. Several factors have been incriminated including patient selection, improved endoscopic technology and superior treatments leading to mucosal healing. What is clear is that the rate of colectomy in UC has decreased which means that more patients get to keep their colon and therefore are theoretically at risk of CRC. In the present review, the authors are reviewing one of the world’s largest and longest-running UC surveillance program from St. Mark’s Hospital in London. This includes data on 1,375 patients with extensive UC who were followed for a median of 11 years. CRC was detected in 72 patients (IR 4.7 per 1,000 patient-years). Although there was a significant decrease in the colectomy rate for dysplasia, the incidence rate of advanced CRC (Duke’s stage C and D) and missed (“interval”) cancers has actually decreased. The IR of dysplasia and early cancer has increased in the most recent decade likely owing to an increased use of chromoendoscopy – which in this study had twice the yield of dysplasia detection compared to white-light colonoscopy. CRC were accompanied by synchronous cancers or multifocal dysplasia in 37.5% of patients. A trove of additional descriptive statistics is available for the interested reader in this data heavy paper: the median UC disease duration at the time of CRC diagnosis was 23.5 years and the median age at CRC diagnosis was 55.5 years. The cumulative incidence of CRC increased steadily after the first decade but reached only 10% after forty years (in a small number of patients followed). The annual IR for CRC after the first decade was relatively constant at 0.4% and the annual IR for any neoplasia (dysplasia + cancer) was 1%. In all, only 61% of cancers had previous history of dysplasia detected as part of surveillance. Among patients sent to colectomy for a finding of HGD at colonoscopy, the rate of cancer in the surgical specimen was 55.5% whereas for LGD it was 28%. There was no increased risk of CRC among patients found to have a “sporadic adenoma” within or outside the area of colitis. There was no significant difference in the risk of progression to CRC between patients with low-grade (LGD) and indefinite for dysplasia. As expected, patients diagnosed with HGD had the highest risk of progression to cancer (15% per year).
Comments: This paper confirms trends from other recent studies including a much lower risk of CRC in long-standing UC than previously estimated. In addition, it indirectly supports the role of chromoendoscopy for dysplasia surveillance. Although the yield of dysplasia and early cancer as part of surveillance seems to be increasing, the incidence of interval cancers which have a poorer prognosis, is decreasing. Also more patients under surveillance are able to keep their colon longer which is an important albeit difficult to measure utility outcome. Chromoendoscopy had a significantly higher negative predictive value compared to white light (WL) colonoscopy: half as many patients diagnosed with HGD or CRC had no dysplasia on previous examinations when surveyed by chromoendoscopy compared with WL HD colonoscopy. There are a number of substantial limitations of this study including selection bias, technological bias (comparison of recent with previous decades in terms of diagnostics and medical treatment), length-time and lead-time bias (surveillance cancers tend to progress slower and provide a spuriously increased survival), lack of information about the type (polypoid, non-polypoid, flat,) location and endoscopic treatment for dysplasia, the impact of chromoendoscopy on the number of biopsies per patient, etc. Nevertheless, given its sheer size and duration, this study provides a unique insight in the epidemiology and outcomes of neoplasia in patients with UC.