The Potential for Medical Therapy to Reduce the Risk of Colorectal Cancer and Optimize Surveillance in Inflammatory Bowel Disease

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KEYWORDS

- Medical therapy • Colorectal cancer • Inflammatory bowel disease
- Surveillance endoscopy

KEY POINTS

- Medical therapy, as in the case of 5-aminosalicylic acid, may have mechanistic plausibility for direct antineoplastic properties, but others, such as thiopurines, do not, suggesting that there is a primary chemopreventive benefit derived from the ability to achieve endoscopic and histologic healing.
- Mucosal healing induced by medical therapy may also provide a secondary preventive benefit by allowing improved endoscopic and histologic detection and differentiation between reactive epithelial changes and dysplasia.
- Of the many risk factors for the development of colitis-associated colorectal cancer (CRC), one of the most modifiable for a treating physician is the presence and severity of chronic inflammation.
- Although the mechanism of the declining risk of CRC in IBD is unclear, the likely determinants are a combination of primary prevention resulting from improved medical therapies able to induce mucosal healing, and secondary prevention derived from improved surveillance endoscopy technologies.

INTRODUCTION

Current goals of therapy for inflammatory bowel disease (IBD) are the induction and maintenance of inflammatory symptoms to provide an improved quality of life, to reduce the need for long-term corticosteroids, and to reduce other long-term outcomes such as disability, hospitalization, and colorectal cancer (CRC).[1] Although the success of this latter goal has been difficult to measure, the overall risk of

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IBD-associated colorectal cancer (CRC) appears to have declined over the past 30 years.[2] The observed decrease in CRC is thought to be due to a combination of factors, including improvements in the ability to identify and to quantify patients at risk and to detect precancerous lesions, and the direct and indirect reduction in cancer resulting from effective medical and surgical therapies of the underlying inflammation.

Some of the well-defined genetic molecular pathways leading to sporadic or hereditary CRC also appear to be present in colitis-associated CRC. However, IBD-associated adenocarcinoma does not seem to follow the discrete adenoma-to-CRC sequence of events.[3] Rather, a progression, from inflamed mucosa to low-grade dysplasia (LGD) to high-grade dysplasia (HGD) to invasive adenocarcinoma, in IBD remains presumed and unproven. In fact, neoplasia in colitis takes different forms, a fact that has resulted in difficulty classifying, identifying, and developing appropriate prevention strategies for it. Cells from colonic mucosa in patients with chronic colitis have the molecular fingerprints of dysplasia and cancer, including genomic instability (aneuploidy), aberrant DNA methylation, and p53 mutations, even before there is any histologic evidence of dysplasia or cancer.[4] It is thought that such a "field effect" of CRC risk is induced by chronic long-standing mucosal inflammation.

Most recently, the degree of inflammation has been shown to be a significant risk factor for neoplasia in IBD.[5,6] In addition to the presence and degree of severity of active endoscopic/histologic colonic inflammation, additional established IBD-associated dysplasia and CRC risk factors include extent and duration of disease, family history of CRC, concomitant primary sclerosing cholangitis (PSC), young age at diagnosis, and presence of postinflammatory polyps and strictures.[4,6] Of these risks, the only modifiable risk factor may be the degree of active inflammation. Therefore, it has been proposed that effective disease control through abrogation of inflammation may also reduce CRC risk in the individual patient.

Although the culmination of this evidence to date supports the clinician-adopted theory that treating to achieve mucosal healing will reduce the risk of CRC in patients with IBD, it remains uncertain how these recommendations can be practically applied by clinicians trying to develop effective dysplasia and CRC prevention strategies in IBD. This article summarizes the potential for medical therapy to reduce the risk of CRC via primary and secondary prevention, and offers practical ways in which a goal of mucosal improvement or healing may be incorporated into clinical practice (**Box 1**).

DEFINITION OF REMISSION IN IBD: AN EVOLVING TARGET

The end point of escalation of therapy in IBD has traditionally been based on adequate symptom control.[7] Despite patient satisfaction in the achievement of clinical

Box 1
Mechanisms by which medical therapy may reduce colorectal cancer in IBD

Primary chemoprevention
Medical therapy reduces inflammation over time
Medical therapy has unique chemoprotection mechanisms
Secondary prevention
Treatment to achieve a healed bowel results in more accurate neoplasia detection by endoscopy
Reduction in histologic inflammation improves pathologist's diagnosis of neoplasia

remission, in many patients this goal is believed to be insufficient in achieving additional goals of stable remission over time and changing the natural history of the disease. In fact, multiple lines of investigation have demonstrated that a significant proportion of IBD patients in clinical (symptomatic) remission continue to have active mucosal inflammation, both endoscopically and histologically.[8] In addition, a prospective study in patients with active colonic or ileocolonic Crohn's disease treated with steroids found no correlation between the clinical activity index and any of the endoscopic data, and although 92% of patients achieved clinical remission, less than one-third of patients also achieved concomitant endoscopic remission.[9]

Clinically the achievement of a healed mucosa has been associated with a modified course of IBD, including a reduction in rates of clinical relapse, fewer inpatient hospitalizations, and decreased lifetime risk of surgery.[10–12] Evidence that a healed bowel mitigates the development of IBD-associated dysplasia and CRC has been insufficient. With the increased interest in endoscopic mucosal healing in clinical trials, it is hoped that additional evidence will demonstrate a direct link between this end point and subsequent reduction in CRC risk. Clinical trials to date have varied definitions ranging from endoscopic resolution of all mucosal ulcerations to endoscopic scoring indices, with very few studies evaluating histologic healing. Therefore, a remaining challenge is this discrepancy between the clinical trials definition of mucosal healing through endoscopic measures and the available evidence related to risk for neoplasia in colitis, which is histologically measured. More recently, the US Food and Drug Administration has expressed interest in histologic assessment of bowel healing, which undoubtedly will lead to additional study and resource allocation.

Nonetheless, as the bar is raised to achieve deeper levels of mucosal healing, one of the significant challenges is the poor correlation between macroscopic mucosal healing as gauged by endoscopic assessment and endoscopist interpretation, and histologically measured disease control as measured by biopsy sampling and pathologist interpretation. In a study of 152 IBD patients in clinical remission undergoing routine surveillance colonoscopy, Baars and colleagues[8] found that only 67% of patients in clinical remission had histologically active inflammation, and of these patients 50% were endoscopically normal. Similarly, in a study of 82 asymptomatic patients with ulcerative colitis (UC), Rubin and colleagues identified that more than 30% of patients had endoscopic inflammation and 89% had histologic evidence of active inflammation.[13] If it is considered that a strict definition of mucosal healing should include resolution of histologic inflammation in addition to an endoscopic assessment of healing, these studies demonstrate the real-world challenge to this approach and emphasize the importance of further study.

A well-described challenge to the use of mucosal healing as a primary end point of the treatment of IBD is the trade-off between risks and benefits (and costs) in patients who feel well, but require escalation of therapy to achieve deeper levels of disease control. It is unclear whether such additional disease control is possible, and whether patients will be willing to escalate their therapy to achieve such control when they are already in clinical remission. Will such dose or class escalation result in more adverse events than benefits? Will it result, as the available evidence thus far suggests, in most patients "burning" through all of the available therapies and never achieving this level of inflammation control? How will the loss of this level of control and so-called disease drift be monitored? How often, and how invasive will repeated assessments be needed? Obviously there remain many unanswered questions before a disease-wide modification in treatment goals can be applied. Nonetheless, there are ongoing efforts to apply a treat-to-target approach used in other chronic diseases to IBD.[14]

Such paradigm shifts in management will answer these questions and guide future therapies.

TREATMENT TO MUCOSAL HEALING MAY IMPROVE DETECTION OF NEOPLASIA IN IBD

Being able to accurately detect precancerous lesions in patients with colonic IBD is requisite for screening colonoscopy and subsequent interval surveillance examinations. IBD-associated colorectal neoplasia may be a challenge to detect endoscopically because it may be multifocal, broadly infiltrating, and arising from flat mucosa, and therefore endoscopically indistinct from the surrounding tissue. Therefore, to adequately sample representative mucosa and identify dysplasia histologically, historical (and current) guidelines endorsed by multiple societies suggest 4-quadrant random biopsy specimens obtained every 10 cm throughout the colon, aiming to obtain at minimum 32 biopsy samples.[15] However, this approach is limited in that it samples less than 1% of colonic surface area and at the same time is subject to poor patient compliance with surveillance, lack of gastroenterologist knowledge, and compliant practice patterns, in addition to poor pathologist interobserver agreement for dysplasia diagnoses.[16,17]

Furthermore, retrospective studies evaluating the visibility of dysplasia and CRC in patients with IBD have found that most dysplastic lesions are endoscopically visible. In a 14-year, retrospective review of 2204 surveillance colonoscopies, Rutter and colleagues[18] found the neoplastic per-lesion and per-patient sensitivity to be 77.3% and 89.3%, respectively. A total of 22.7% of lesions were macroscopically invisible on colonoscopy. A 10-year, single-institution, retrospective study by Rubin and colleagues[19] in the United States similarly found dysplasia or cancer had per-lesion and per-patient endoscopic visibility of 61.3% and 76.1%, respectively. In this series, 38 of 65 dysplastic lesions (58.5%) and 8 of 10 cancers (80.0%) were visible to the endoscopist as 23 polyps and masses, 1 stricture, and 22 areas of irregular mucosa. In this series 38.7% of lesions were endoscopically invisible, detected only by random biopsy. These retrospective studies did not account for the advent of newer advances in colonoscopic technology, including high-definition or image-enhancement endoscopy techniques such as chromoendoscopy, all of which are believed to further improve visualization and guide future preventive approaches.

In the setting of macroscopically active inflammation, the pathologic diagnosis of dysplasia is often more challenging, primarily because of the difficulty in differentiating inflammation-associated regenerative changes and true dysplasia. In the setting of healing UC, epithelial regeneration occurs with changes that may mimic dysplasia, especially in the eyes of the less experienced pathologist. The epithelial cells become cuboidal with eccentric, large nuclei, mucin depletion, and prominent nucleoli.[20] As a result, pathologists may need to interpret such biopsy specimens as “indefinite for dysplasia” or undiagnosable for dysplasia. Therefore, in addition to the pursuit of mucosal healing as a method of primary prevention of dysplasia and CRC, its achievement may also provide benefit in secondary prevention of CRC, defined as the accurate detection of existing precancerous lesions by gastroenterologists and pathologists. Completing a surveillance colonoscopy in the setting of mucosal healing should improve visualization of neoplastic lesions for the endoscopist, and improve the ability of pathologists to distinguish regenerative change from true dysplasia.

MEDICAL THERAPY AS PRIMARY CHEMOPREVENTION IN IBD-ASSOCIATED NEOPLASIA

The pathophysiology of colitis-associated dysplasia and cancer have implicated the molecular products of chronic inflammation from both innate and adaptive immune

cells in the development of a risk-increasing "field effect" of genetic changes in IBD-associated neoplasia.[21] This relationship is supported by the severity of histologic inflammation as an independent risk factor for neoplastic progression.[22,23] In addition to directly reducing inflammation, medical therapy may play a primary chemopreventive role, altering the molecular pathways to dysplasia development (**Box 2**).

5-Aminosalicylates

With demonstrated clinical efficacy and favorable safety profile, 5-aminosalicylic acid (5-ASA) derivatives are the foundational first-line therapy for the induction and maintenance of mild to moderate ulcerative colitis. In addition to the clinical benefit of their anti-inflammatory mechanism, advances in understanding the mechanisms of action reveal multiple molecular chemopreventive properties, including: promotion of cell-cycle arrest to increase the stability of the genome and DNA replication fidelity; inhibition of lipoxygenase and cyclooxygenase-2 (COX-2), thereby regulating angiogenesis via prostaglandin synthesis; scavenging of free radicals and reactive oxygen and nitrogen species to reduce DNA oxidative stress and microsatellite instability; and induction of expression of peroxisome proliferator-activated receptor γ (PPAR-γ), a potent tumor suppressor that interferes with canonical Wnt/β-catenin activity for prevention of CRC.[24–26]

Since 5-ASA was first linked with a reduction in the risk of colitis-associated cancer in 1994,[27] there have been multiple retrospective cohort and case-control observational studies with differing results. In 2005, a systematic review and meta-analysis of 9 observational studies and 1932 patients concluded that there was a protective association between 5-ASA use and cancer (odds ratio [OR] 0.51; 95% confidence interval [CI] 0.37–0.69), and between 5-ASA and cancer and dysplasia (OR 0.51; 95% CI 0.38–0.69).[28] However, since that time, 5 and case-control studies with a larger population cohort have published data that are discordant, demonstrating no protective association.[29–33] The largest of these, using the Manitoba IBD epidemiology database, found no protective benefit in those using 5-ASA therapy for 1 year or longer and 5 years or longer based on a cohort of 8744 IBD patients (OR 1.04, 95% CI 0.67–1.62 and OR 2.01, 95% CI 1.04–3.9, respectively) and a case-control population of 404 CRC patient (OR 1.02, 95% CI 0.60–1.74 and 1.96, 95% CI 0.84–4.55, respectively).[30] Similarly, in a more recent meta-analysis that focused on nonreferral studies to reassess the role of 5-ASA for CRC protection, Nguyen and colleagues[34] found no protective benefit, with a pooled adjusted odds ratio of 0.95 (95% CI 0.66–1.38) and moderate study heterogeneity (I^2 = 58.2%; P = .07).

The clinical evidence is hindered by the inherent imperfections of an observational, retrospective investigation, including patient heterogeneity in disease duration and extent, study design and data sources, and monitoring compliance and concomitant medical therapy. There is molecular mechanistic reasoning supporting the use of 5-ASA in colitis-associated cancer prevention, and although the clinical observational studies to date have yielded discrepant results, the 2010 American

Box 2
Potential chemoprotective agents in IBD-associated dysplasia and colorectal cancer

5-Aminosalicylic acid

Thiopurine

Anti–tumor necrosis factor antibodies

Gastroenterological Association technical review favored, with moderate certainty, that 5-ASA is chemopreventive against CRC.[35] Although it remains a point of contention, the overall safety of these therapies has resulted in many clinicians continuing their use even when other drugs are used for disease control, even if only because of the possibility of such secondary benefit.

Thiopurines

Systemic immunomodulators including the traditional thiopurines, 6-mercaptopurine (6-MP) and its nitroimidazole derivative, azathioprine (AZA), are purine synthesis inhibitors used in a primary and adjunctive role for the maintenance of remission in patients with both Crohn's disease and UC, in addition to the prevention of immunogenicity against monoclonal antibody therapies, including anti–tumor necrosis factor (TNF)-α and anti-integrin inhibitors. Whereas 5-ASA derivatives have biological mechanisms of action rationalizing their potential role as chemopreventive agents, thiopurines' lack of evidence demonstrating direct antineoplastic mechanisms to suggest any benefit in reducing the risk of dysplasia or CRC may be due to their established anti-inflammatory effects.

Initial studies evaluating the chemopreventive benefits of thiopurines had discrepant results, with most demonstrating no benefit in chemoprevention (but also no increased risk of cancer). In 2010, the available literature was insufficient evidence for the American Gastroenterological Association to make recommendations for or against the use of thiopurines as potential chemopreventive agents.[36] However, recent clinical studies have provided sufficient evidence to reconsider the potential for 6-MP and AZA to reduce the risk of colitis-associated dysplasia and CRC in patients with IBD.

Two large population-based cohorts, similar to prior studies, had different results. In a Dutch cohort of 2578 patients with IBD, van Schaik and colleagues[33] reported that 28 patients (1%) developed HGD or CRC during 16,289 person-years of follow-up. Two of 28 patients (7%) were on thiopurines alone and 1 patient (of 28, 4%) was on a thiopurine plus 5-ASA. Thiopurine use was associated with a significantly decreased risk of developing HGD or CRC with an adjusted hazard ratio (HR) of 0.10 (95% CI 0.01–0.75). However, Pasternak and colleagues[37] found no protective benefit in a Danish cohort of 45,986 IBD patients, of which 11% were on AZA (adjusted relative risk [RR] = 1.00; 95% CI 0.61–1.63).

In 2013, the first prospective study of the epidemiology of colorectal HGD and cancer in IBD in the thiopurine era was published by Beaugerie and colleagues.[38] The results of the CESAME (Cancers Et Surrisque Associé aux Maladies Inflammatoires Intestinales En France) trial, a French nationwide observational cohort of 19,486 patients with IBD designed in the early 2000s to assess the risks of any cancer or HGD in IBD patients, found that 57 (0.3%) patients developed HGD or CRC during the follow-up period (37 CRC, 20 colorectal HGD). In patients with long-standing, extensive colitis, defined as disease duration of at least 10 years and extent of at least 50% of the colon, the multivariate adjusted HR for colorectal HGD and CRC was 0.28 for those who received thiopurines (95% CI 0.1–0.9; $P = .03$).

In the study of inflammation risk by Rubin and colleagues,[5] multivariate analysis identified thiopurine exposure as a significant predictive factor (adjusted OR 0.25; 95% CI 0.08–0.74). This finding, after controlling for degree of inflammation, was one of the strongest lines of evidence to date.

A meta-analysis pooling of 19 studies (9 case-control and 10 cohort studies), while acknowledging high heterogeneity among studies ($I^2 = 68.0\%$, $P<.001$), reported that the use of thiopurine was associated with a statistically significant decreased

incidence of CRC or dysplasia (HGD and LGD) with a pooled RR of 0.71 (95% CI 0.54–0.94; $P = .017$), even after adjustment for duration and extent of the disease.[39] In the thiopurine-treated patients, the RR of HGD and CRC was 0.72 (95% CI 0.50–1.03; $P = .070$) and 0.70 for CRC (95% CI 0.46–1.09; $P = .111$).

Despite these recently published reports demonstrating a reduced risk of dysplasia and CRC with thiopurine use, any derived chemopreventive benefit is likely to remain adjunctive to standard clinical indications for use. Given its known risk profile, lack of plausible biological mechanism, success of surveillance colonoscopy, and, possibly, increased anti-inflammatory benefit from anti–TNF-α antibodies, unlike 5-ASA therapies, thiopurines are very unlikely to be recommended as a pure chemopreventive agent in isolation.

Anti–TNF-α Antibodies

Anti-TNF agents are able to induce and maintain mucosal healing in the subset of patients with moderate to severe UC and Crohn's disease, and as a result are likely providing additional chemopreventive benefits by reducing long-standing chronic inflammation. In addition, early investigations into the molecular mechanisms of TNF-α in colitis have suggested a possible direct antineoplastic role from TNF blockade. Using an in vivo dextran sulfate sodium (DSS) and azoxymethane mouse model for chronic colitis–induced cancer, Popivanova and colleagues[40] identified an increase in the levels of TNF-α and infiltrating leukocyte TNF receptor in the colonic mucosa and submucosa before the development of colonic tumors. Treating the mice with a human TNF-α antagonist, etanercept, resulted in decreased tissue injury, and low levels of inflammatory infiltrate and neutrophil-derived and macrophage-derived chemokines. Tumors were reduced in number and size and had poor angiogenesis, presumably from the suppressed COX-2 expression.

The few studies that evaluate the efficacy of anti-TNF agents to reduce the risk of colitis-associated dysplasia and cancer have discordant findings. In a Dutch nationwide, nested case-control study of 173 cases of IBD-associated CRC from 1990 to 2006, the use of anti-TNF (OR 0.09, 95% CI 0.01–0.68; $P = .02$) was significantly protective for the development of CRC. However, in a nationwide population-based Danish cohort, there was no significant difference in the risk of colitis-associated CRC in IBD-exposed patients when compared with nonexposed patients (adjusted RR 1.06; 95% CI 0.33–3.40).

Ursodeoxycholic Acid

Patients with a concomitant diagnosis of UC and PSC remain at a very high risk for the development of dysplasia and CRC. Ursodeoxycholic acid (UDCA) is a synthetic bile acid that has been proposed to have a molecular mechanism that can reduce the risk of dysplasia and CRC by decreasing the colonic concentration of bile acids, inhibiting Ras gene mutations and COX-2 expression, and having antioxidant activity. In a prospective, randomized, placebo-controlled trial of UDCA therapy in 52 patients with UC and PSC, 10% of patients receiving UDCA developed CRC versus 35% of patients not on UDCA therapy, resulting in a significant RR of 0.26 for developing colorectal dysplasia or cancer (95% CI 0.06–0.92; $P = .034$).[41] However, this prospective study has been countered by several studies reporting that long-term high-dose (28–30 mg/kg daily) UDCA is not protective in UC or PSC patients, and instead may increase the risk of colorectal neoplasia.[42] Therefore, at present the use of UDCA for chemoprotective reasons alone is not recommended.

A Proposed Approach to the Patient with Ongoing Mucosal Inflammation

With mucosal healing now entrenched as a clinical trial end point and significant evidence demonstrating that mucosal healing modifies the course of the disease, including potentially reducing the risk of cancer via primary and secondary prevention, one question that remains is how is this new paradigm best applied in the clinic? Key issues include how patients in clinical remission should be monitored, and what a clinician should do when active inflammation is encountered on surveillance endoscopy.

Assessment of the mucosa and success at achieving healing requires interval evaluation of the bowel, and current evidence further favors histology. This approach implies the need for repeat endoscopic assessment, which has limitations in cost and patient acceptance. Although endoscopy for dysplasia detection is effective and continually improving with technology, the invasiveness, lack of resources, and, probably, cost-ineffectiveness precludes the performance of endoscopy (and biopsies) every 3 to 6 months from the time of diagnosis. Therefore, surrogate markers of mucosal healing, including blood-based and stool-based biomarkers and noninvasive, nonradiation imaging techniques will remain a focus of continued investigation. For example, the use of neutrophil-derived fecal markers, including calprotectin and lactoferrin, has been positively correlated with endoscopic and histologic activity.[43] The key clinical consideration is that baseline determinations of these noninvasive assessments must be obtained and correlated with endoscopic findings to provide meaning to changes over time. In addition, the timing intervals for monitoring remain unclear. Extrapolating from primary clinical trials evaluating mucosal healing, it is known that in the case of anti–TNF-α agents by week 6 to 8, mucosal healing rates (Mayo endoscopic subscore or equivalent score 0–1) were 42.3% to 62.0% in UC,[41,44–46] and by weeks 10 to 12 were 27% to 31% in Crohn's disease.[47,48] An important point is that in all of the UC trials, the maintenance rates of mucosal healing were all similar to or lower than that at the induction time point, suggesting that surrogate evaluation as frequently as every 8 weeks could indicate a change in mucosal healing.

For now, the most frequent question that arises is related to the performance of routine (guideline-based) surveillance in the asymptomatic patient and the unanticipated inflammation. First, it is important to determine whether the findings are due to an alternative cause such as infection with *Clostridium difficile* or cytomegalovirus. In the setting of true active inflammation, the clinician should reassess the patient's symptoms (or lack thereof) and adherence to the existing regimen of therapy, as often patients will self-discontinue or self-reduce a dose without a discussion with their provider; this is especially true when the patient is feeling well. When patients are truly compliant with therapy and in clinical remission but have endoscopic inflammation, it is reasonable to optimize the existing therapies as an initial step. This approach may include maximizing therapy within the same class of therapies, which can be achieved via therapeutic drug monitoring with thiopurine metabolites or serum monoclonal antibody levels, in addition to determination of antidrug antibodies. After any interval change in therapy, reassessment of the mucosa to determine success is reasonable. The timing of such reassessment is based on the likelihood that a therapeutic adjustment does affect change, which and may occur after 3 to 6 months. Endoscopic or acceptable surrogates may be used to evaluate change. Only after optimization of current therapies has been attempted would it be appropriate to discuss the relative benefits and risks of stepping up to the next class of therapy. Patient acceptance of this approach is critical to implementation (**Box 3**).

A similar approach might be used for patients who desire an alternative or complementary therapy for their IBD. In such unproven therapies, a negotiated trial of the

Box 3
Optimization options for the patient who is not healed (without needing to change class of therapy)

Assess Compliance with Current Regimen

5-ASA

- Dose or delivery response
- Increase dose
- Add rectal therapy

Thiopurine

- Assess metabolite profile
- Dose increase
- If shunting, consider allopurinol

Anti-TNF: immunogenicity is a risk

- Dose increase
- Consider levels and antibody assessment
- Switch within class

therapy and interval assessment of mucosal healing or other objective benefit can be very helpful for the patient, the clinician, and the so-called therapeutic alliance between them. When such therapeutic trials succeed (or not), an informed discussion about making treatment changes can occur.

FUTURE APPROACHES

Although the incidence of CRC in IBD appears to be decreasing, the mechanism for this decline remains unclear. Significant gaps in the literature remain regarding how clinicians may enhance primary and secondary prevention of colitis-associated dysplasia. There currently is no standard definition of mucosal healing. While clinical trial literature has elected to use any one of the many endoscopic scoring systems, evidence points to persistent histologic inflammation in the setting of endoscopic quiescence. It is theorized that persistent histologic inflammation will increase the risk of CRC, but aggressive efforts to change medical therapy in pursuit of this end point carry both long-term and short-term risks of side effects for an unproven benefit. A unified definition of inflammation control (endoscopic, histologic, radiologic, or other) would allow for better comparison of the efficacy of medical therapy for the induction and maintenance of mucosal healing, in addition to the disease-modifying long-term outcomes, including the risk of colitis-associated CRC.

There is limited to no information about the success of a combination random and targeted surveillance approach to detection of dysplasia, and little has been written about the interval improvement in inflammation control that may also improve detection and prevention. Finally, given the logistical challenges and inherent flaws of retrospective case-control and cohort studies, coupled with the significant number of patients and duration of follow-ups required for prospective CRC prevention studies, it may be best to continue to promote investigation in patient adherence to therapy and compliance to recommended guidelines for surveillance.

In the absence of direct evidence of cancer benefit, the movement of research in IBD toward control of mucosal inflammation as a disease-modifying end point seems

sufficient to continue to pursue improved disease control and, secondarily, to anticipate reduced neoplasia as a downstream result.

SUMMARY

Medical therapy, as in the case of 5-ASA, may have mechanistic plausibility for direct antineoplastic properties, but others, such as thiopurines, do not, suggesting that there is a primary chemopreventive benefit derived from the ability to achieve endoscopic and histologic healing. Mucosal healing induced by medical therapy may also provide a secondary preventive benefit by allowing improved endoscopic and histologic detection and differentiation between reactive epithelial changes and dysplasia.

Of the many risk factors for the development of colitis-associated CRC, the only modifiable one for a treating physician is the presence and severity of chronic inflammation. Over the past 20 years, significant progress has been made with the use of agents capable of mucosal healing, and during this time the risk of CRC in IBD patients has declined. Although the mechanism of the declining risk of CRC in IBD remains unclear, the likely determinants are a combination of primary prevention from improved medical therapies able to induce mucosal healing, and secondary prevention from improved surveillance endoscopy technologies.

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