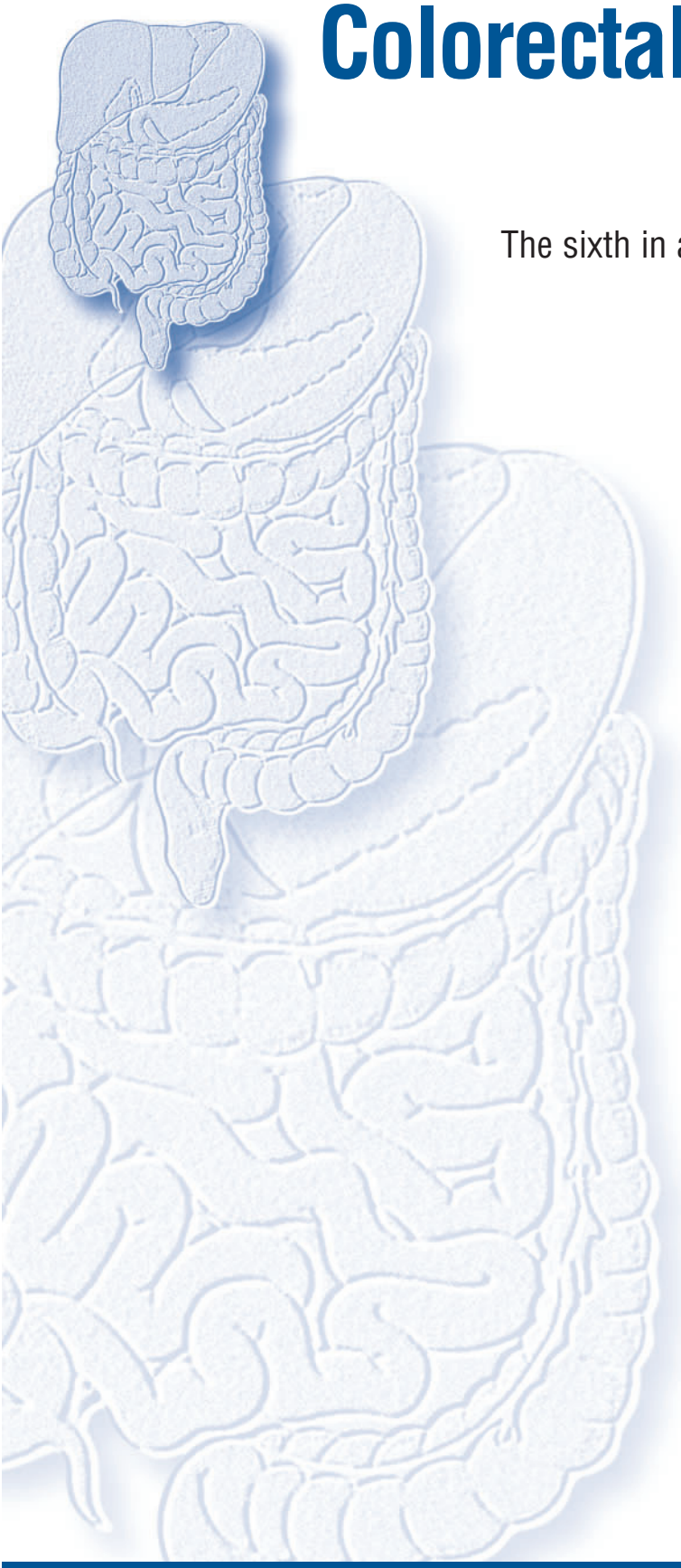
The State of the Art in the Management of Inflammatory Bowel Disease:

Update and Recent Advances in Colorectal Cancer Prevention



The sixth in a series of educational newsletters

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mesalamine	Asacol® Pentasa® Rowasa® Canasa®		
olsalazine sodium	Dipentum®		
balsalazide disodium	Colazal™		
Sulfasalazine	Azulfidine®	Ulcerative colitis	Crohn's disease and chemoprevention of colorectal cancer in IBD
NSAIDs, Aspirin	Various	Various	Chemoprevention of colorectal cancer

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THE STATE OF THE ART IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE: Update and Recent Advances in Colorectal Cancer Prevention

INTRODUCTION

This *Clinical Courier®, The State of the Art in the Management of Inflammatory Bowel Disease,* is the sixth in a series of publications; it represents an update to the proceedings of a roundtable that was held with an esteemed faculty in Washington, DC. Inflammatory bowel disease (IBD) is a serious, idiopathic disease that manifests as ulcerative colitis (UC) or Crohn's disease (CD), both characterized by chronic and relapsing inflammation of the intestines. Significant morbidity associated with both forms of IBD is linked to the disease itself and also to serious, life-threatening complications, particularly colorectal cancer (CRC). Although the prevalence of CRC among patients with IBD has been identified more commonly in those afflicted with UC, those with CD also have an increased risk of CRC.[1] Despite controversy regarding the incidence in CD of CRC, there is evidence that the malignant potentials in CD and UC are of similar magnitude.[2] Moreover, mortality among patients with underlying IBD who develop CRC is higher than for those who develop sporadic CRC.[2] Management goals for IBD must therefore include steps to minimize the risk of CRC development. The 5-aminosalicylic acid (5-ASA) compounds are the cornerstone of IBD treatment—as induction and maintenance therapy for mild-to-moderate UC and for quiescent CD—for both their established efficacy and tolerability. Recent data have provided promising evidence that long-term maintenance therapy with 5-ASAs confers protection against CRC for patients with IBD.[3]

This publication will focus on the incidence and risks of CRC in IBD; the efficacy and safety of the 5-ASAs and their proposed mechanisms as chemopreventive agents for CRC; adherence issues in the treatment of IBD and the reasons adherence is important; and the controversy over treatment of low-grade dysplasia (LGD) in IBD. These issues are equally relevant to both men and women with IBD.

EDUCATIONAL OBJECTIVES

By the end of this program, participants should be able to discuss and summarize the:

- Efficacy and safety of 5-ASA compounds in the management of inflammatory bowel disease (IBD)
- Major risk factors for colorectal cancer (CRC) in patients with IBD
- Recent study data supporting the use of 5-ASAs in preventing CRC in IBD
- Proposed mechanisms of action of mesalamine in preventing CRC
- Risks of nonadherence to IBD treatment, and techniques to promote treatment adherence to prevent life-altering complications
- Controversy regarding the treatment of low-grade dysplasia; surgical vs medical management

CRC IN PATIENTS WITH IBD

Incidence of CRC

The first case of cancer in IBD, reported by Crohn and Rosenberg in 1925, was one of ulcerative colitis-associated rectal cancer.[4] The risk of CRC for patients with IBD is somewhat difficult to quantify, partly because of the relative rarity of IBD in the general population. Nevertheless, incidence data from case reports and population-based studies have confirmed the risk of IBD-related CRC. The absolute cumulative frequency of colorectal cancer in patients with extensive colitis—8% at 22 years from onset of symptoms for CD and 7% at 20 years from onset of symptoms for UC—attest to significant occurrence in both forms of IBD.[5] This serious sequela of IBD accounts for 1 of every 6 deaths among IBD patients.[2] Most experts agree that CRC risk does not begin until about 8 to 10 years after the UC diagnosis, increasing thereafter by 0.5% per year in the second decade and 1.0% per year in the third.[6] For patients with CD, the risk of malignancy is not as well defined.[6] Friedman et al reported on their longitudinal study of 233 patients with extensive Crohn's colitis who had undergone periodic biopsies from 1980 to 1998. They concluded that the cumulative incidence of neoplasia paralleled that reported in extensive UC.[7]

A study by Bernstein et al evaluated the risks of various cancers for IBD patients compared with matched non-IBD cohorts over a 14-year period. There was an increased incidence rate ratio of colon cancer for both UC patients (2.75) and CD patients (2.64). Patients with UC, but not CD, had an increased incidence rate ratio of rectal cancer, whereas patients with CD, but not UC, had an increased incidence rate ratio of cancer of the small intestine.[8] These findings support previous studies citing the risk of CRC for patients with IBD.[1,9-11]

The State of the Art in the Management of Inflammatory Bowel Disease is the sixth in a series of publications, and it represents an update to the proceedings of a roundtable that was held in Washington, DC. Learning objectives of that roundtable were as follows:

By the end of the program, participants were able to discuss what is known about sex differences in IBD patients and to summarize current findings and identify knowledge gaps as they apply to the

- Epidemiology and proposed etiologies of ulcerative colitis and Crohn's disease
- Clinical and diagnostic findings in adults and children with inflammatory bowel disease
- Clinical utility of traditional and evolving therapies in the everyday management of ulcerative colitis and Crohn's disease
- Psychosocial challenges IBD patients face
- Relationship between adherence and disease relapse to optimize adherence in clinical practice

Statement of Need: Inflammatory bowel disease (IBD) is a serious, idiopathic disease that manifests as ulcerative colitis (UC) or Crohn's disease (CD), both characterized by chronic and relapsing inflammation of the intestines. Significant morbidity associated with both forms of inflammatory bowel disease is linked to the disease itself and also to serious, life-threatening complications, particularly colorectal cancer (CRC). Therefore, the management of IBD should address both symptom remediation and long-term sequelae, with particular emphasis on the importance of maintaining disease remission and on reducing the risk of CRC. It is important that physicians have a thorough understanding of the importance of adherence to first-line pharmacotherapies and of the current and emerging means of primary and secondary prevention of CRC for their patients with either UC or CD.

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CRC Risk Factors Associated With IBD

Several independent factors have been suggested as major risks for the development of CRC for patients with IBD.[12-14] These include

- Disease duration
- Extent of colonic involvement
- Severity of colonic inflammation
- Young age at onset of IBD
- Presence of primary sclerosing cholangitis (PSC)
- Positive family history of CRC (particularly early-onset CRC)

In a retrospective study, Eaden and colleagues determined the independent effects of various risk factors on the odds ratio of developing colonic cancer (Table 1).

The overall risk of CRC for patients with IBD increases with increasing duration of disease. According to a meta-analysis, the cumulative risk of developing CRC in UC corresponded to 2% by 10 years, 8% by 20 years, and 18% by 30 years[15] (Figure 1). The extent of disease also greatly contributes to the risk of CRC development. In a population-based cohort study of 3117 patients diagnosed with UC, Ekbom et al observed that

TABLE 1

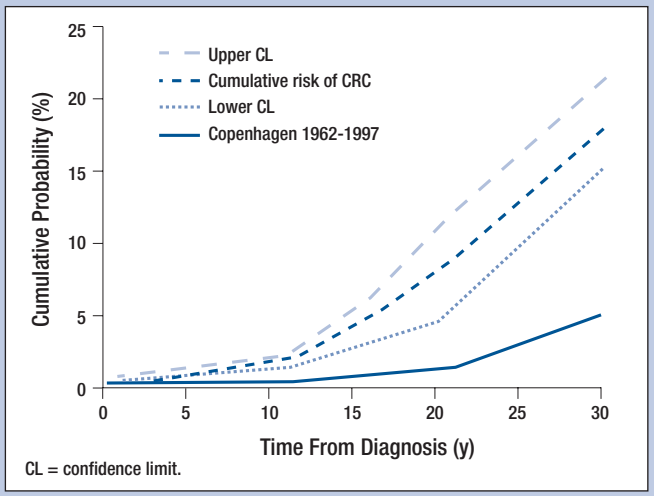
Adjusted Odds Ratios for Most Influential Variables for Colorectal Cancer Risk

Variable	Odds Ratio	95% CI	*P* Value
No 5-ASA treatment	—	—	—
Any 5-ASA treatment	0.47	0.22-1.00	.05
Mesalamine			
<1.2 g/day	0.18	0.02-1.92	.16
≥1.2 g/day	0.19	0.06-0.61	.006
Sulfasalazine			
<2 g/day	0.93	0.22-3.91	.92
≥2 g/day	0.85	0.32-2.26	.75
Other (olsalazine, balsalazide)			
Variable doses	1.21	0.08-18.97	.89
Contact with physician			
0	—	—	—
1-2/year over the course of disease	0.42	0.15-1.18	.10
>2/year over the course of disease	0.16	0.04-0.60	.007
CRC in any relative			
No	—	—	—
Yes	6.84	0.80-58.60	.08
Colonoscopies after diagnosis			
0	—	—	—
1-2 over the course of disease	0.33	0.11-1.01	.05
>2 over the course of disease	0.55	0.18-1.71	.30

CI = confidence interval.
Adapted with permission from Eaden J, et al. *Aliment Pharmacol Ther*. 2000;14:149.

FIGURE 1

Cumulative risk of developing CRC in UC



CL = confidence limit.

Adapted with permision from Munkholm P. *Aliment Pharmacol Ther.* 2003;18:2.

patients with ulcerative proctitis had an incidence ratio of 1.7, those with left-sided colitis had an incidence ratio of 2.8, and those with pancolitis had an incidence ratio of 14.8.[16]

The severity of colonic inflammation has also been recently identified as a risk factor for patients with long-standing extensive UC. Rutter et al, in a case control study (N = 136), concluded that "in long-standing extensive UC, the severity of colonic inflammation is an important determinant of the risk of colorectal neoplasia."[14]

CRC risk is also increased for patients diagnosed with IBD at an earlier age. Patients whose CD was diagnosed before age 30, with any colonic involvement at diagnosis, had a 10-fold higher relative risk of CRC than did those diagnosed at later ages.[1]

Patients with UC accompanied by PSC have an approximately 5-fold higher risk of CRC than do UC patients without this concomitant disorder. For UC patients with PSC, in one study, the absolute risk of developing CRC or dysplasia was 9% after 10 years of disease, 21% after 20 years, and 50% after 25 years, compared with 2%, 5%, and 10%, respectively, in UC controls without PSC (P<.001).[17] A retrospective cohort study of 178 patients with well-documented PSC showed an increased CRC risk relative to the general U.S. population only during the period in which UC coexisted with PSC. The investigators hypothesized that if PSC is an additional risk factor for neoplasia in UC, the clinical significance of this risk appears to be low[18]; however, the authors pointed out that their study design did not enable them to prove or disprove this hypothesis.

Although a positive family history of CRC is associated with a 2- to 3-fold risk for CRC development for persons with sporadic, noncolitic CRC, few studies have been performed assessing this risk for patients with UC.[17] A case-control study found that a family history of sporadic CRC was an independent risk factor for cancer in UC, with CRC being more than twice as frequent among UC patients with family histories than among UC controls.[19] A large, population-based cohort study of patients with IBD confirmed that information on family history of CRC, particularly with early onset, may facilitate identification of individuals with IBD at high risk for CRC.[13]

5-ASAs: TRADITIONAL AND CONTEMPORARY TREATMENT APPROACHES IN IBD

The first ASA compound, sulfasalazine, which was developed in the 1940s, consists of sulfapyridine bonded to mesalamine (5-ASA). Sulfasalazine is cleaved by colonic bacterial azo-reductases into sulfapyridine and the 5-ASA moiety. The 5-ASA moiety is the anti-inflammatory component of sulfasalazine, whereas sulfapyridine acts as a carrier for 5-ASA and accounts for most of the drug's toxicity.[20] The dose-limiting side effects associated with sulfasalazine prompted the development of sulfa-free ASA preparations, which may be given in higher doses without the risk of increased toxicity. The 5-ASAs, available in oral and topical formulations, are the treatment of choice for mild-to-moderate disease and are selected according to the anatomic extent of disease and its clinical severity (Figure 2).[20] For extensive disease, the 5-ASAs are administered orally, and for distal disease, they are administered orally and/or rectally.[21]

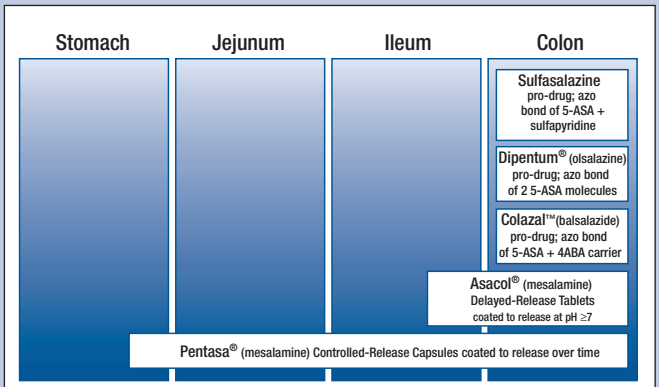
Efficacy of 5-ASAs in IBD Management

Given the similar pharmacokinetic profiles of the various mesalamine preparations,[22] important factors that influence individual product selection include efficacy, toxicity, dose response, and adherence to dosing and schedules. As a class, the oral 5-ASAs are equally effective for induction of remission in active UC and have clinical efficacy similar to that of sulfasalazine in the treatment of active and quiescent UC.[20] At dosages of 2 to 6 g/day, sulfasalazine leads to improvement or remission for two thirds of patients with mild-to-moderate UC; maintenance of remission is achieved by 75% of patients with UC with 2 to 4 g/day of sulfasalazine,[20] although many patients may be unable to tolerate the higher dosage.[21] Meta-analyses of 5-ASA as maintenance therapy in CD reported relapse-free rates of 68% to 95% with dosages of 1.5 to 3 g/day.[20] The efficacy of mesalamine increases over the dosage range,[20] and it is important to continue adequate dosages of this drug to maintain remission.

The primary goals of maintenance therapy in IBD are to prolong periods of remission and optimize quality of life. Once remission has been achieved, it is important to consider the dose response and route of administration of the primary maintenance agents, the aminosalicylates. Historically, the 5-ASA dosage used for remission induction was often reduced when

FIGURE 2

Oral sulfasalazine and 5-ASA preparations: formulations and sites of delivery



patients began maintenance therapy; however, the current standard of care of some physicians for patients taking mesalamine is to continue with the induction dosage.[21] The efficacy of both sulfasalazine and mesalamine is dose related—the dose response for mesalamine actually begins at what would be the most effective maintenance dosage of sulfasalazine (4 g/day). Although the recommended dosage of mesalamine is 2.4 g/day,[23] clinical experience has shown that higher maintenance dosages, up to 4.8 g/day, provide efficacy without compromising tolerability.[21] A meta-analysis of the literature that examined treatment options for UC reported a 92% remission maintenance rate among patients treated with oral mesalamine 3.2 g/day, compared with 78% among those treated with olsalazine 1 g/day, or 60% among those treated with 2 g sulfasalazine, suggesting superior remission maintenance rates with higher doses.[24] In the first trial that demonstrated clinical improvement or remission for mesalamine-treated patients with CD, 43% of patients achieved remission after 16 weeks of mesalamine 4 g/day, compared with 18% of placebo patients (*P*=.007). In that study, efficacy was clearly dose related—23%, 24%, and 43% of mesalamine-treated patients achieved remission at daily doses of 1 g, 2 g, and 4 g, respectively.[25]

Tolerability of 5-ASAs

The toxicity of the parent compound should be considered in the choice of a 5-ASA. At higher effective doses, systemic absorption of the sulfapyridine component of sulfasalazine is associated with troublesome side effects that include headache, epigastric pain, nausea, vomiting, and oligospermia.[21,26] As noted previously, the sulfa-free 5-ASA preparations such as mesalamine allow delivery of higher doses without concomitant increases in systemic toxicity. A meta-analysis of various 5-ASA compounds revealed a strikingly similar adverse-event rate between patients treated with 5-ASA compounds (31%) and placebo-treated patients (33%).[27] A recent systematic review examining the safety of 5-ASAs in UC revealed that adverse-event rates for patients treated with short-term mesalamine therapy were similar to those with placebo and lower than those seen with sulfasalazine, although the use of olsalazine in a dose-dependent fashion resulted in diarrhea for some patients.[28]

Efficacy of 5-ASA Compounds in Preventing CRC

The chronic inflammatory nature of IBD predisposes patients with this disease to a higher risk of developing CRC. Studies indicate that chronic or repeated episodes of mucosal inflammation occurring in IBD may result in carcinogenesis based on several mechanisms, including genetic mutations, changes in epithelial cell metabolism, increased epithelial cell turnover, alterations in enterohepatic circulation, and changes in bacterial flora.[29] Therefore, reducing the duration and severity of chronic inflammation with an anti-inflammatory agent that has chemopreventive potential is an important consideration of long-term treatment. Prevention of colorectal adenomas with regular aspirin use has been well documented in the medical literature.[30,31] Recent clinical evidence indicates that the 5-ASA compounds, chemically similar to aspirin, may have a chemopreventive effect in IBD and suggests that regular use of these agents over the disease course may lessen the likelihood of CRC development.

Several clinical studies have confirmed the efficacy of 5-ASA in reducing the risk of CRC for patients with IBD. In a retrospective, case-control study (although there were differences between various 5-ASA formulations and dosages), regular use of any 5-ASA was associated with a 75% risk reduction for CRC (*P*<.00001). In contrast, the benefits of sulfasalazine were less pronounced, with an effect evident only at a dosage of ≥2 g/day.[3] After adjusting for other variables, mesalamine ≥1.2 g/day was the only treatment associated with a statistically significant reduction in the risk of developing cancer (81%; *P*=.006).[3] Results of this study also demonstrated that (considering variables independently), IBD patients with positive family histories of sporadic CRC have a 5-fold relative increased risk of CRC.

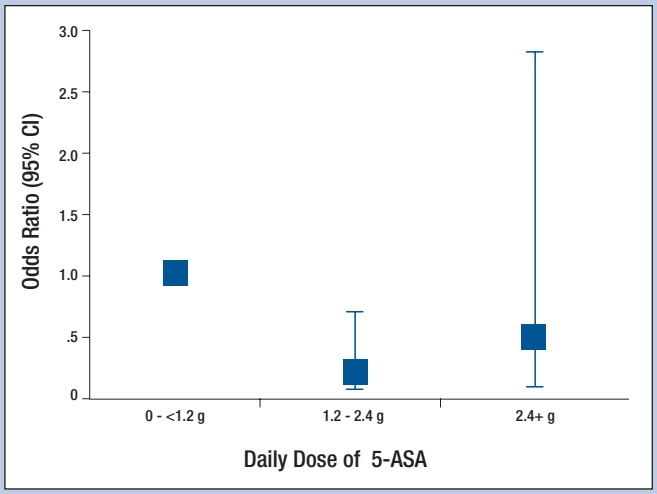
Rubin and colleagues evaluated the effect of 5-ASA use on the risk of dysplasia and CRC for patients with UC. Twenty-six patients with dysplasia (n = 18) or CRC (n = 8) were matched to 96 controls (UC without dysplasia or CRC). Cases and controls were closely matched for age, gender, age at UC diagnosis, and duration and extent of disease. Cases were more likely to have family histories of CRC than were controls (27% versus 9%, respectively, *P*=.036). Treatment with at least 1.2 g/day of mesalamine was associated with a risk reduction of 72% and an odds ratio of 0.28 for dysplasia or CRC (Figure 3, *P*=.024). As the total dose of mesalamine increased, the odds of dysplasia or CRC decreased significantly, which supports a chemopreventive effect of 5-ASA in UC.[32]

A further study evaluated the effect of 5-ASA dose on the progression from early-grade dysplasia (defined as flat indefinite dysplasia or flat LGD) to more advanced neoplasia (high-grade dysplasia [HGD] or CRC) in UC. Retrospective analysis identified 82 patients with UC and early-grade dysplasia; 46 patients received 5-ASA therapy of 0 to <2 g/day (labeled "low-dose" for study purposes), and 36 patients received 5-ASA therapy of ≥2 g/day (labeled "high-dose"' for study purposes). These dosage were labeled *low* and *high* for study purposes.[33] (In actual clinical practice, treatment must be individualized for each patient, and dosages of mesalamine of up to 4.8 g/day have been observed to be effective, with no dose-related adverse effects.[20])

Overall, 14 patients (17%) progressed to advanced neoplasia; patients taking "high-dose" 5-ASAs (n = 5) had the slowest rate of progression (Figure 4). The findings of this study suggest that 5-ASA may act early in the colitis-dysplasia-carcinoma sequence, thus delaying the rate of progression to advanced neoplasia, and that higher-dose 5-ASA may

FIGURE 3

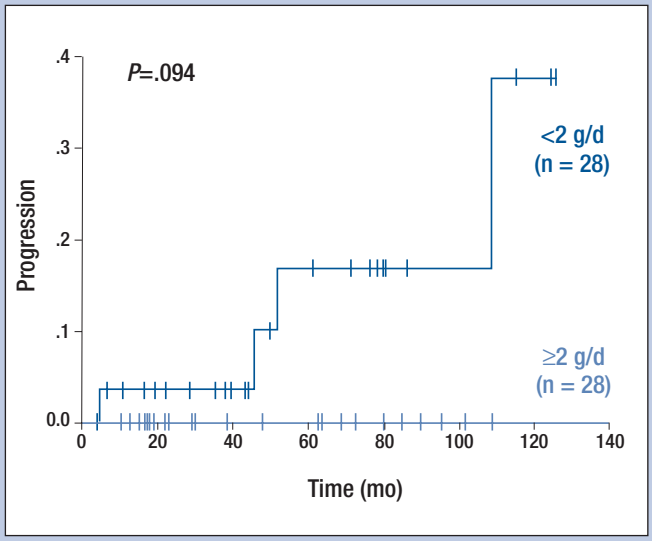
Odds ratio of dysplasia and CRC vs dosage of 5-ASA



Rubin D, et al. Abstract presented at Digestive Disease Week; May 17-22, 2003; Orlando, Fla.

FIGURE 4

Effect of 5-ASA therapy on progression of indefinite dysplasia in patients with UC



Adapted with permission from Croog V, et al. Poster presented at Digestive Disease Week; May 17-22, 2003; Orlando, Fla.

confer chemoprotection to patients with indefinite dysplasia. For patients with LGD at diagnosis, however, the use of 5-ASA is not likely to offer significant protection against disease progression, and progression is likely to occur regardless of treatment strategy.[33]

Bernstein and colleagues conducted a population-based study to determine whether the use of 5-ASA was associated with a reduced risk of CRC among patients with IBD. In contrast to the chemopreventive role of 5-ASAs described above, the results of this study did not support such a role. The authors concluded that because 5-ASA use could only be assessed for 2 to 4 years before the diagnosis of CRC, a repeat study in the future using a larger sample size and a longer duration of 5-ASA use would be helpful. It is possible that use of 5-ASA late in the disease does not have a protective effect against neoplasia but that long-term 5-ASA use initiated early in the course of IBD may have such an effect. The authors further suggested that case-control studies from diverse populations would provide the most valid data concerning the relationship between 5-ASA therapy and prevention of CRC. They speculated that if future studies confirm the use of 5-ASA as being of benefit for reducing CRC incidence, an important issue would be patient adherence to therapy.[34]

Chemopreventive Mechanisms of NSAIDs

Epidemiologic studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) possess significant anti-CRC properties, although the mechanism by which they exert these effects is controversial.[35] Experimental evidence indicates that NSAIDs induce apoptosis, inhibit cellular proliferation, and inhibit the formation of colorectal polyps and tumors.[36] The NSAIDs are well known to inhibit cyclooxygenase-2 (COX-2), which is involved in the conversion of arachidonic acid to prostaglandin. COX-2 has been observed to be upregulated in colon cancer.[35] The anti-CRC effects of NSAIDs are achieved through both COX-2–dependent and –independent mechanisms, but inhibition of the COX-2 pathway is theorized to be the primary mechanism by which NSAIDs arrest the development of sporadic CRC.[37] Another COX-independent anticancer mechanism thought to be associated with NSAIDs involves inhibition of nuclear factor κβ, which is increased in CRC and has strong antiapoptotic effects.[36]

Chemopreventive Mechanisms of the 5-ASAs/Mesalamine

The 5-ASAs are structurally similar to the NSAIDs, although these 2 classes of drugs differ in function. The 5-ASAs do not possess the COX-2–inhibiting properties of the NSAIDs; however, they are thought to exert certain anticancer effects through common COX-2–independent pathways.[36] The mechanism of the presumed chemopreventive effect of mesalamine is not well understood, although it likely involves this agent's anti-inflammatory action and/or inhibition of arachidonic acid, a prostaglandin precursor. Recent research and clinical work have suggested that mesalamine may have inhibitory properties comparable to those of other NSAIDs.[38] For example, strong inhibition of nuclear factor κβ activation was demonstrated in biopsy specimens from mesalamine-treated patients with UC.[39] Tissue samples taken from mesalamine-treated patients with CRC demonstrated significant apoptosis of cancer cells with no concomitant effect on the apoptotic index in normal epithelium.[40] In intestinal epithelial cells of mice, mesalamine reversed the antiproliferative effects of tumor necrosis factor alpha, a regulatory cytokine, and inhibited its activation of nuclear factor κβ.[41]

ADHERENCE ISSUES IN THE TREATMENT OF IBD

Both forms of IBD are characterized by periods of active disease interspersed with remission, and both require long-term treatment. Patients with these diseases tend to take their prescribed medication only when they are acutely ill, and are frequently nonadherent to medication during periods of quiescence.[42] When a patient enters remission, a "honeymoon phase" is often experienced—as the remission progresses, the patient may begin to question the validity of maintenance therapy, believing that he/she can "do just fine" without any medication. Although data may be somewhat contradictory with regard to the factors related to IBD relapse, there appears to be agreement that the following are contributors:

- Medication nonadherence
- Inadequate doses of maintenance therapy
- Adverse reactions to medications
- Emotional stress

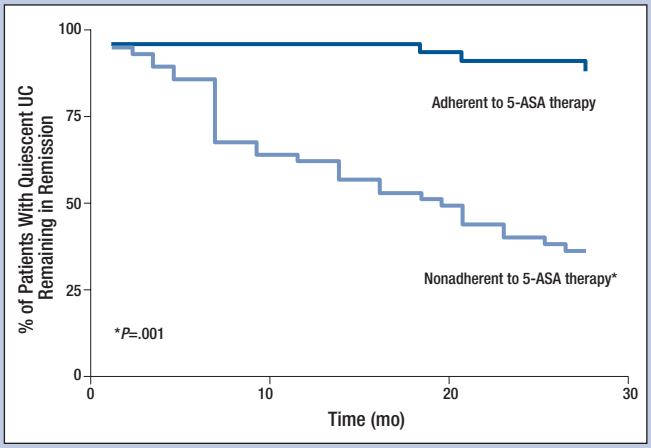
Medication nonadherence was evaluated in a prospective cohort study of 99 patients taking maintenance mesalamine for quiescent UC. As illustrated in Figure 5, page 6, nonadherence was associated with significant relapse rates. Overall, patients who were adherent to treatment had an 89% chance of maintaining remission compared with a 39% chance for those who were nonadherent (*P*=.001).[43]

Factors That Influence Adherence

The issue of adherence to IBD treatment presents specific challenges to both patients and their physicians. Factors that influence adherence may be classified as related to 1) the disease, 2) the patient, 3) and the treatment itself.

FIGURE 5

Nonadherence is associated with relapse in UC



Adapted from *Am J Med*., Vol. 114, Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis, pages 39-43, Copyright 2003 with permission from Excerpta Medica.

Disease Issues

The extent, duration, and severity of disease are factors that affect a patient's adherence to treatment. It appears that in cases where the disease course is fraught with numerous flare-ups, patients are much more likely to adhere to treatment. Conversely, patients who have fewer flare-ups, and thus longer remission cycles, may be less likely to continue maintenance therapy.

Patient Issues

Patients who are well informed about their disease and treatment are generally more adherent. Responses to a questionnaire that assessed how well informed IBD patients (50 with UC and 50 with CD) believed themselves to be indicated that 64% of UC patients and 76% of CD patients considered themselves insufficiently informed about their disease. Although 91% of these patients indicated that educational materials prepared specifically to meet their needs could be very useful, 35% indicated that knowledge of the risks of their disease might increase their anxiety.[44] Specific patient-related factors that influence adherence include degree of education received from healthcare providers, comprehension of instructions for appropriate use of medication, understanding of the potential consequences of nonadherence, extent of self-management skills, and strength of the patient's support system.[42] Interestingly, gender and marital status of the patient with IBD are also factors that influence adherence. In a study that assessed nonadherence to mesalamine treatment among 94 outpatients with quiescent UC, only 40% of patients adhered to their treatment regimens. Nonadherent patients were more likely to be male, single, and have UC confined to the left side. Additionally, nonadherence was associated with multiple concomitant medications (>4 prescription medications).[45]

Treatment Issues

Factors related to treatment that are most likely to influence adherence are efficacy, tolerability, and convenience. The 5-ASA compounds are virtually comparable in maintaining remission in mild-to-moderate UC; however, because it lacks the sulfa moiety contained in sulfasalazine, mesalamine can be given in higher doses without the increased risk of intolerability. Convenience factors related to medication therapy include the number and size of tablets/capsules, delivery method, and dosing regimen. Findings of a recent study that evaluated medication nonadherence by patients with IBD suggested that an increased risk of intentional nonadherence was associated with shorter disease duration, not scheduling follow-up appointments, lack of certainty that medication would be helpful, and greater total patient-physician discordance. Overall findings suggest that effective communication between patient and physician influences medication adherence positively.[46]

Promoting Adherence to IBD Treatment to Prevent Life-Altering Complications

Perhaps the key to optimal adherence lies in therapy individualization, which takes into account the patient's disease and therapeutic history, response to previous medications, history of adherence to previous treatment regimens and scheduled visits, and medication costs. Educating patients about the chronicity of their disease, and thus the need for continued treatment, is crucial to promoting adherence. Other possible ways physicians can help promote treatment adherence include the following:

- Discuss with patients which treatment regimens and side effects they can and cannot tolerate, and prescribe accordingly. For some patients, having to take frequent enemas will lead to nonadherence; however, a randomized, double-blind study found that combination mesalamine therapy (once-daily oral plus twice-weekly enemas) was more effective than oral therapy alone in maintaining remission of UC, with lower relapse rates at 12 months.[47]
- Simplify the medication regimen when possible. For example, oral mesalamine can be taken bid, tid, or qid, depending on patient preference and schedule.[42] Kane et al conducted a small, randomized pilot trial to assess the short-term outcomes of once-daily dosing of mesalamine versus conventional dosing in maintaining remission in UC. The authors concluded that patients taking once-daily mesalamine had outcomes similar to those for patients on conventional regimens.[48]
- Emphasize to patients that adhering to the maintenance dose of an anti-inflammatory such as mesalamine may decrease the risk of CRC.
- Help patients adhere to schedules of surveillance colonoscopy by explaining the value of this procedure in detecting precancerous changes.
- Consider the psychosocial and emotional dynamics of each patient when prescribing. For example, adolescents and college students may be more prone to nonadherence because of various social pressures and issues of privacy.

THE CONTROVERSY OVER TREATMENT OF LGD IN IBD: SURVEILLANCE COLONOSCOPY OR COLECTOMY?

Patients with long-standing and extensive colitis are at considerable risk for the development of CRC. An association between dysplasia in flat rectal mucosa and carcinoma for patients with UC was identified more than 35 years ago,[49] although the definition, diagnosis, and grading of LGD in flat, colitis-involved mucosa remains varied. At present, no universal consensus has been reached regarding the optimal treatment of IBD patients with LGD.

Surveillance Colonoscopy

Surveillance colonoscopy is a widely accepted method of colon cancer prevention in the general population that has extended to the area of IBD. The theory of surveillance colonoscopy postulates that dysplasia represents a halfway point on the continuum from colitis to cancer.[50] Lim and Axon support regular follow-up of patients with long-standing extensive UC in remission, with or without flat LGD, maintaining that early colectomy should be reserved for patients with dysplasia-associated lesions or masses (DALMs) or HGD.[51] No randomized, controlled trials have been performed that prove the benefit of surveillance colonoscopy; however, retrospective analyses have examined this preventive approach.

A meta-analysis of 10 prospective studies of patients with UC undergoing dysplasia surveillance reported that 1.9% of 798 evaluable patients had HGD at initial screening surveillance colonoscopy, and 8.6% had LGD. Of 51 patients with indefinite dysplasia at initial colonoscopy, 18% were later found to have HGD, DALM, or cancer, and 27 (28%) of 95 patients who had indefinite dysplasia at some point during surveillance were subsequently found to have HGD, DALM, or cancer.[52] A retrospective analysis of 46 UC patients with flat LGD showed unexpected advanced neoplasia (either HGD or cancer) in 23.5% of patients who underwent colectomy and who had not demonstrated progression previously. On an actuarial basis, the rate of progression to advanced neoplasia for all 46 patients with flat LGD was 53% at 5 years (Figure 6). Results of this study suggest that a finding of flat LGD during UC surveillance colonoscopy is a strong predictor of advanced neoplasia.[53]

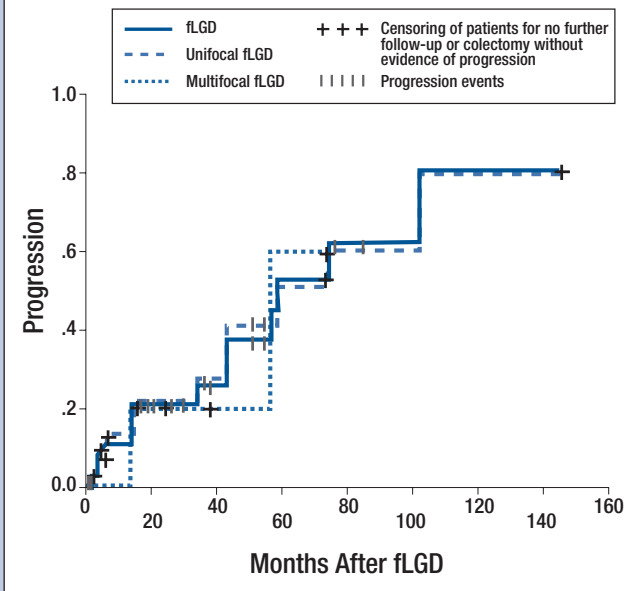
Colectomy

Ullman recommends that all UC patients with flat LGD at surveillance colonoscopy undergo colectomy for the following reasons: 1) patients may already harbor CRC by the time LGD is discovered; 2) the actuarial neoplastic progression rate is as high as 54% at 5 years; 3) LGD may progress to CRC during surveillance; and 4) there are no accurate markers of progression for patients with LGD. Limitations of surveillance colonoscopy include lack of commitment and diligence among patients, and poor understanding by gastroenterologists of the meaning and prognostic features of dysplasia. Ullman argued that dysplasia is actually indicative of neoplasia and that the potential risks of choosing to delay surgery ultimately outweigh the benefits of delaying it.[54]

Befrits et al questioned the recommendation of immediate colectomy for patients with long-standing IBD and LGD in flat mucosa. Sixty such patients were followed for a mean of 10 years (LGD was detected at the screening colonoscopy in 20 of these patients and during subsequent colonoscopic surveillance in the remaining 40). The authors concluded that although LGD was confirmed on repeated colonoscopies in 73% of patients, no progression to HGD was found (with the exception of 2 patients with DALMs, one of whom had HGD on biopsy and underwent subsequent colectomy). However, the authors believed that they could not rule out the possibility that any of 13 patients in the study who underwent colectomy might have developed cancer without surgery. They concluded that the finding of DALM and HGD during surveillance of one patient and the discovery of an adenocarcinoma in another patient who had multifocal LGD in flat mucosa in several previous colonoscopies demonstrate the importance of vigilant colonoscopic surveillance of IBD patients.[55]

FIGURE 6

Kaplan-Meier curve comparing cumulative progression to advanced neoplasia for patients with any, unifocal, and multifocal flat LGD



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Although most treatment centers recommend proctocolectomy for confirmed LGD and HGD or for DALM complicating preexisting UC, this approach is not completely supported by the literature. This is based on the argument that the risk of CRC appears to be no greater than if LGD is discovered in a patient monitored by an appropriately conducted surveillance program than it is for a person whose surveillance biopsy results were indefinite for dysplasia.[56]

CONCLUSION

The strong potential for development of CRC in both UC and CD necessitates careful therapeutic choices to minimize this risk. The 5-ASA compounds—the cornerstone of IBD treatment—appear to have a chemoprotective effect against the development of CRC in IBD, although the exact mechanism by which the 5-ASAs confer this effect is not entirely clear. Recent clinical evidence suggests that consistent use of 5-ASA compounds, particularly mesalamine, in IBD is associated with considerable reduction in CRC risk and a delayed rate of progression to dysplasia/carcinoma. Awareness of issues surrounding CRC prevention in IBD, such as the arguments, both pro and con, concerning surveillance colonoscopy versus surgery and the factors that affect treatment adherence, will allow clinicians to help their patients with IBD make and adapt to treatment choices that will be most likely to prevent life-altering complications.

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THE STATE OF THE ART IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE: Update and Recent Advances in Colorectal Cancer Prevention

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1. Which of the following statements are true regarding the epidemiology of CRC?
   a. Mortality for patients with underlying IBD who develop CRC is higher than for those who develop sporadic CRC.
   b. CRC accounts for 1 in 6 of all deaths among patients with IBD.
   c. The risk of CRC begins about 5 years after the diagnosis of UC.
   d. a & b
   e. All of the above

2. Which of the following are considered risk factors for the development of CRC for patients with IBD?
   a. Positive family history of CRC
   b. Extent of colonic involvement
   c. Young age at onset
   d. Long disease duration
   e. All of the above

3. The severity of colonic inflammation has been identified as a risk factor for colorectal neoplasia in UC.
   a. True b. False

4. Each of the following statements pertaining to dosing of 5-ASAs is true EXCEPT
   a. The dose response for sulfasalazine begins at what would be the highest dose of mesalamine.
   b. The efficacy of sulfasalazine and mesalamine is dose related.
   c. Mesalamine may be given in doses up to 4.8 g/day without compromising tolerability.
   d. Clinical trials have shown that efficacy rates were nearly doubled for patients who took mesalamine 4 g/day compared with those who took 2 g/day.

5. Although surveillance colonoscopy and prophylactic colectomy are considered approaches to management of LGD, no universal consensus has been reached regarding which one is optimal.
   a. True b. False

6. One of the most important clinical considerations for long-term treatment of IBD is
   a. Prescribing combination topical and oral 5-ASA therapy to all patients with IBD
   b. Including an anti-inflammatory agent with chemopreventive potential
   c. Ensuring that patients with IBD undergo colonoscopy annually following diagnosis
   d. None of the above

7. Ways in which physicians can help promote treatment adherence by IBD patients include:
   a. Individualize IBD therapy for each patient
   b. Consider the psychosocial and emotional dynamics of each patient
   c. Simplify the medication regimen when possible
   d. All of the above

8. For patients with IBD, regular 5-ASA use at a dosage of at least 2 g/day has been shown to:
   a. Slow the progression of indefinite dysplasia to advanced neoplasia
   b. Slow the progression of low-grade dysplasia to advance neoplasia
   c. Slow the progression of high-grade dysplasia to CRC
   d. Block the progression of CRC

9. Which of the following statements are true regarding the efficacy of 5-ASA compounds in CRC prevention?
   a. Mesalamine is associated with a statistically significant reduction in the risk of CRC development.
   b. 5-ASA appears to act early in the colitis-dysplasia-carcinoma sequence.
   c. Among patients with UC, dysplasia or CRC development was found to be inversely proportional to the mesalamine dose.
   d. The benefits of sulfasalazine in reducing the risk of CRC were less pronounced than were those of mesalamine.
   e. All of the above

10. The current approach of some physicians for maintaining remission in patients with IBD taking mesalamine is to continue the same dosage used for remission induction.
    a. True b. False

Please record your posttest answers: 1.____ 2.____ 3.____ 4.____ 5.____ 6.____ 7.____ 8.____ 9.____ 10.____

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THE STATE OF THE ART IN THE MANAGEMENT OF INFLAMMATORY BOWEL DISEASE:
Update and Recent Advances in Colorectal Cancer Prevention

