

• REVIEW •

5-aminosalicylic acid is an attractive candidate agent for chemoprevention of colon cancer in patients with inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is classically subdivided into ulcerative colitis (UC) and Crohn's disease (CD). Patients with IBD have increased risk for colorectal cancer. Because the pathogenesis of colorectal carcinoma has not been entirely defined yet and there is no ideal treatment for colon cancer, cancer prevention has become increasingly important in patients with IBD. The two adopted methods to prevent the development of colon cancer in clinical practice include the prophylactic colectomy and colonoscopic surveillance. But patients and physicians seldom accept colectomy as a routine preventive method and most patients do not undergo appropriate colonoscopic surveillance. Chemoprevention refers to the use of natural or synthetic chemical agents to reverse, suppress, or to delay the process of carcinogenesis. Chemoprevention is a particularly useful method in the management of patients at high risk for the development of specific cancers based on inborn genetic susceptibility, the presence of cancer-associated disease, or other known risk factors. Prevention of colorectal cancer by administration of chemopreventive agents is one of the most promising options for IBD patients who are at increased risks of the disease. The chemopreventive efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) against intestinal tumors has been well established. But with reports that NSAIDs aggravated the symptoms of colitis, their sustained use for the purpose of cancer chemoprevention has been relatively contraindicated in IBD patients. Another hopeful candidate chemoprevention drug for IBD patients is 5-aminosalicylic acid (5-ASA), which is well tolerated by most patients and has limited systemic adverse effects, and no gastrointestinal toxicity. 5-ASA lacks the well-known side effects of long-term NSAIDs use. Retrospective correlative studies have suggested that the long-term use of 5-ASA in IBD patients may significantly reduce the risk of development of colorectal cancer. According to the literature, this agent might well satisfy clinical expectations with respect to a safe and effective chemopreventive agent.

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INTRODUCTION

Inflammatory bowel disease (IBD) is classically subdivided into ulcerative colitis (UC) and Crohn's disease (CD). In some instances, these diseases have a few overlapping clinicopathologic features^[1]. Colorectal cancer is a prominent cause of morbidity and mortality in Western countries^[2-4]. The pathogenesis of colorectal carcinoma is not entirely defined yet although some progress has been made. Furthermore, there is still no effective treatment for advanced or metastatic carcinoma in clinical practice to date^[5]. Patients with IBD have long been reported to have an increased risk for colorectal cancer, but the quantitation of the risk of colorectal cancer in this specific population varies widely in different studies^[1,6-8].

Ekbom *et al*^[9] investigated a population-based cohort of 3117 patients with UC from 1922 through 1983, the observation time ranged from 1 to 60 years after diagnosis. The incidence of colorectal cancer in this cohort showed an increase. [standard incidence ratio (SIR): 5.7]. The SIR was 1.7 for ulcerative proctitis, 2.8 for left-sided colitis, and 14.8 for pancolitis, as compared with the general population. The absolute risk of colorectal cancer 35 years after diagnosis was 30% for patients with pancolitis at diagnosis and 40% for those who were diagnosed before the age of 15 years. The risk factors, which are important in the development of colorectal cancer in UC include extent of disease, duration of disease, severity and time course of inflammation, age of onset, a positive family history of sporadic colon cancer, *etc.*

Unlike UC, which is associated with colorectal cancer reported as early as in the 1920s, it has long been thought that CD is not associated with gastrointestinal cancer^[10,11]. But in 1990, Ekbom *et al*^[12] reported a population-based study in which the increased relative risk of colorectal cancer in patients with CD was confirmed. They also found that patients with CD who were diagnosed before the age of 30 with colonic involvement at diagnosis had a higher relative risk (20.9) than those diagnosed at older ages (2.2). Choi *et al*^[13] reported similar results to Ekbom's, but other reports did not find any association between CD and colorectal cancer^[14,15].

Thus from the literature it appears that patients with either UC^[6-8] or CD^[12,13] have an increased risk for colorectal cancer compared with general population although there are different opinions about CD patients^[10,11,14,15].

TREATMENT AND PREVENTION OF COLON CANCER

Because there is still no ideal treatment for colon cancer and the survival rate low (<50%) 5-year survival rate A^[13], cancer prevention has become an increasingly important consideration in IBD. The two adopted methods^[16] to prevent the development

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of colon cancer by gastroenterologists are the prophylactic colectomy and colonoscopic surveillance. Although the most effective strategy to prevent colorectal cancer in high-risk patients with UC is prophylactic colectomy, patients and physicians are generally unwilling to accept colectomy as a routine preventive method. The second widely adopted method is colonoscopic surveillance. Despite evidence that early detection by fecal occult blood tests and colonoscopic surveillance can decrease the risk of death due to colorectal cancer, most patients do not undergo appropriate screening. Furthermore, a few reports have shown conflicting results and these studies^[17,18] suggest that surveillance leads to the detection of early-stage cancer in only a minority of patients and a significant number of patients develop cancer at an advanced stage despite surveillance.

Because of ethical reasons and patient compliance, it is difficult to perform randomized, controlled trials in order to define the role of surveillance colonoscopy in colorectal cancer prevention. No sufficient evidence^[17,18] shows that surveillance is truly efficacious and cost effective in preventing death from colorectal cancer. Delco *et al*^[19] studied a hypothetical cohort of patients with UC. The benefits of life years saved were weighted against the costs of biannual colonoscopy and proctocolectomy, and the terminal care of patients dying of colorectal cancer. Two separate Markov processes were modeled to compare the cost-benefit relation in patients with or without surveillance. The cumulative probability of developing colorectal cancer served as a threshold to determine which of the two management strategies was associated with a larger net benefit. In the end they concluded that it was not possible to prove that frequent colonoscopies at regular intervals were effective to manage the increased risk of colorectal cancer associated with UC. Medical decision analysis failed to show that surveillance colonoscopy would be beneficial to patients with UC. Although it is a widely accepted fact that patients really benefit from screening colonoscopy and colonoscopic pursuits of newly developed symptoms or suspicious findings, it is difficult to prove that frequent colonoscopies at regular intervals is an effective means to manage the increased risk of colorectal cancer associated with UC.

The most effective strategy to prevent colorectal cancer is prophylactic colectomy but it is seldom accepted as a routine preventive method^[16]. Considering the real effect, risk, expense, and sampling error of endoscopic surveillance, it is not an ideal preventive approach to cancer control^[17-19] either. Therefore, the development of safer and more effective methods for reducing the risk of colorectal cancer would be of substantial benefit to IBD patients and attract many researchers' attention and interest. The most attractive method is perhaps to chemoprevent colon cancer using specific drugs.

Chemoprevention of colon cancer by NSAIDs in IBD patients and its limitation

Chemoprevention^[20,21] or chemoprotection refers to the use of natural or synthetic chemical agents to reverse, suppress, or to delay the process of carcinogenesis. Chemoprevention is a particularly useful method in the management of patients at high risk for the development of specific cancers based on the inborn genetic susceptibility, the presence of cancer-associated diseases, or other known risk factors.

According to the knowledge that prostaglandins (PG) are trophic agents for gastrointestinal epithelial cells, many researchers^[22-24] have initiated researches focusing on the potential chemopreventive effects resulting from aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). The chemopreventive efficacy of NSAIDs against intestinal tumors has been well established. Many studies over the past decade

have demonstrated that NSAIDs have a potent inhibitory effect on the growth of colorectal cancer. Positive results reported that indomethacin, piroxicam, and sulindac as well as aspirin could significantly reduce tumor incidence. It is postulated that this antitumor effect is mediated through reduction in PG production, most notably PGE₂, which is frequently overexpressed in intestinal tumor tissues. But recent studies indicate some NSAIDs might exert their chemoprotective effect through a PG-independent apoptotic mechanism.

At first it was hoped that NSAIDs could be used widely in patients with IBD, but with reports that NSAIDs aggravated the symptoms of colitis, their sustained use for the purpose of cancer chemoprevention has been relatively contraindicated in IBD patients. The long-term use of NSAIDs is associated with significant toxicity. Data from observational studies and randomized controlled trials indicates that there are risks of aspirin use even at small doses^[25]. Gastrointestinal conditions such as dyspepsia, peptic ulcer disease, and gastrointestinal hemorrhage are exacerbated by aspirin and other NSAIDs^[26,27]. Thus, there is a need to identify alternative chemopreventive agents that are more appropriate for use in IBD patients as well as other NSAID-intolerant, high-risk cancer groups.

5-aminosalicylic acid and its epidemiological data in IBD-associated colon cancer patients

Another candidate chemoprevention drug for IBD patients is 5-aminosalicylic acid (5-ASA)^[28], an anti-inflammatory drug that has been used extensively in the treatment of IBD for more than 50 years and is well tolerated by most patients and has limited systemic adverse effects, and gastrointestinal toxicity^[29]. Orally ingested plain 5-ASA is rapidly and completely absorbed in the upper gastrointestinal tract. The systemic availability of 5-ASA is low, because it is rapidly metabolized, mainly at the gut mucosa, to pharmacologically inactive metabolite N-acetyl-5-aminosalicylate^[28]. 5-ASA thus lacks the well-known side effects of long-term NSAIDs use. This could make it an attractive candidate agent for the chemoprevention of colorectal carcinoma at current scientific level.

5-ASA is a therapeutically active ingredient of sulphasalazine and sulphapyridine simply acting as a carrier to ensure that the active part is released within the bowel. A number of different delivery systems and formulations of 5-ASA have been developed^[28]. These are either sulphapyridine-free azobond analogues of sulphasalazine, such as olsalazine, or enteric-coated (delayed release) or slow release 5-ASA (mesalazine) preparations, such as Pentasa, Asacol, and Salofalk. Olsalazine has been shown to be poorly absorbed in the small intestine and reaches the colon intact, where it is activated into two molecules of 5-ASA. Balsalazide^[30] is a prodrug that links the aminosalicylate 5-ASA to the carrier 4-aminobenzoyl β -alanine via an azo-bond. The 5-ASA component is then liberated in the colon via the action of bacterial azoreductases. Pentasa microgranules are coated with a semipermeable membrane of ethylcellulose. Because of the amphoteric properties of ethylcellulose, 5-ASA is slowly released from the granules into the intestine continuously over time, that enhances with pH above 6.0. The aim of different formulations is to get a high intraluminal colonic concentration and a low systemic load of 5-ASA. In theory, the enteric-coated formulation seems more attractive because of the reduced systemic load of the unsplit compound and its sulphated metabolite^[28].

Several retrospective correlative studies^[31-33] have suggested that the long-term use of 5-ASA in IBD patients may significantly reduce the risk of development of colorectal cancer. Pinczowski *et al*^[31] found that in a population-based cohort of 3 112 patients with UC, pharmacological therapy, especially sulfasalazine,

lasting for at least 3 mo was associated with a significant protective effect on colon cancer by calculating relative risk through conditional logistic regression. Eaden *et al*^[32] designed a retrospectively matched case-control investigation study. They collected medical records of suitable patients in England and Wales. One hundred and two cases met the inclusion criteria and were matched with controls from the Leicestershire IBD patient database. A suitable model was developed to assess the contribution of the variables in a forward selection procedure. Conditional logistic regression was used to compute estimates of odds ratio (OR) as a measure of association between various exposures and colorectal cancer. The most significant finding was the strong protective association of regular 5-ASA therapy, reducing cancer risk by 75% (OR 0.25, 95% CI: 0.13-0.48, $P < 0.00001$). When individual 5-ASA drugs and their doses were analyzed, mesalazine at a dose of 1.2 g/d or greater reduced colorectal cancer risk by 91% compared to no treatment (OR 0.09, 95% CI: 0.03-0.28, $P < 0.00001$) and was also protective when taken at lower doses (OR 0.08, 95% CI: 0.08-0.85, $P = 0.04$). The benefits of sulphasalazine were less pronounced and the effect was only evident at a dose of 2 g/d or greater (OR 0.41, 95% CI: 0.41, 95% CI: 0.18-0.92, $P = 0.03$). Other 5-ASA medications also had a non-significant protective effect. They concluded that the benefit of regular consumption of 5-ASA was equal to frequent visits to a hospital physician.

Moody *et al*^[33] conducted a retrospective study. One hundred and seventy-five patients diagnosed between 1972 and 1981 with colitis were identified and formed a 10-year cohort whose cancer risk was assessed in 1992. The cumulative incidence of colorectal cancer 10 years after diagnosis was 2.1% and 20 years after diagnosis was 7.4% for the total group of patients excluding those with a colectomy. They demonstrated that patients with UC who did not comply with 5-ASA therapies were significantly more likely to develop colorectal cancer than their counterparts. The crude proportion developing cancer were 3% (5/152) in the group who took long-term 5-ASA, but 31% (5/16) in the group who had their treatment stopped or did not comply with therapy ($\chi^2 = 20.2$, $df = 1$, $P < 0.001$).

Research progress in the mechanism of 5-ASA in chemoprevention of colon cancer

The exact mechanism by which 5-ASA acts has not yet been fully elucidated. Drugs that liberate 5-ASA in the colon can reduce cancer risk by reducing inflammation or by an effect analogous to that of NSAIDs in normal subjects and patients with adenomatous polyposis. A few studies^[34,35] suggest that 5-ASA might act by blocking the transcription factor, nuclear factor kappaB (NF- κ B), by upregulating or stabilizing its natural inhibitor I κ B, while others^[36] have found no evidence for an influence of 5-ASA on NF- κ B pathway.

Bus *et al*^[37] conducted a prospective pilot study in patients with colorectal cancer. In the biopsies from malignant and normal tissues before and after treatment with 1 g/d mesalazine enemas for 14 d, they found that the apoptotic score increased significantly in the tumor samples while the cell proliferation in malignant tissue was not affected by mesalazine. However, Reinacher-Schick *et al*^[5] found that mesalazine not only significantly induced apoptosis but also decreased proliferation in colorectal mucosa in patients with sporadic polyps of the large bowel. Apoptotic index showed a significant increase in 1 and 3 d after initiation of treatment with mesalazine as compared with controls. Proliferation appeared to be decreased by mesalazine in all treatment groups, while proliferation in controls did not change. This pharmacological effect of 5-ASA on colorectal cell homeostasis may result in a shift towards cell loss, leading to net tissue mass reduction. MacGregor *et al*^[38]

reported that 5-ASA had anti-proliferative effects on human colon cancer cell lines (LS174T, HT-29, LoVo, HRT-18). Results of FACS analysis of LS174T cells indicated that 5-ASA produced a 35% increase in the proportion of cells in G0/G1 and a concomitant decrease in the proportion of cells in S phase. But balsalazide did not alter the cell cycle distribution. They also studied the effect of 5-ASA and balsalazide on the apoptosis of LS174T cells and found 5-ASA inhibited proliferation of colon cancer cells and induced apoptosis. But other studies have failed to show a significant antiproliferative effect of 5-ASA against HT-29, SW480, and DLD-1 colon cancer cells in culture^[39] or against colon tumors in an azoxymethane-induced rat model^[40].

It seems that 5-ASA does not exert its anti-inflammatory effect by inhibiting the enzyme cyclo-oxygenase. Potential mechanisms^[41] for its antiinflammatory effects include: scavenging of oxygen-derived free radicals, inhibition of lipoxygenase, modulation of the prostaglandin profile by an effect on prostaglandin 15-hydroxydehydrogenase, and interference with leukocyte function.

MacGregor *et al*^[38] studied the effect of balsalazide on an animal model for colon cancer, in which the chemical carcinogen azoxymethane (AOM) induced preneoplastic colonic lesions termed aberrant crypt foci (ACF), which later progressed to carcinomas. ACF were induced in Fischer 344 rats via 2 subcutaneous injections of AOM (20 mg/kg). They found balsalazide treatment of AOM-injected rats reduced ACF formation in a dose-dependent manner by 60%. This was proved in another model of 1,2-dimethylhydrazine (DMH)-treated rats. Brown *et al*^[41] reported that 5-ASA reduced the number of ACF by over one-third, effectively reduced tumor number and load, increased the rate of tumor apoptosis, and reduced the rate of tumor cell proliferation.

Another widely used genetic animal model of colon cancer is the *Min/+* mice, which develop intestinal neoplasia. This model was generated by treatment of C57BL/6J mice with ethylnitrosourea followed by selection for transmission of germline mutations. A fully penetrant dominant mutation was identified that predisposed these mice to spontaneous adenomas throughout the intestinal tract. Ritland *et al*^[21] failed to observe the effect of 5-ASA on tumor number in *Apc*^{Min} mice. They studied several formulations of 5-ASA (free acid, sulfasalazine, and Pentasa) at multiple oral dosage levels in *Apc*^{Min} mice; although each of these formulations was shown to deliver maximal 5-ASA concentrations to different regions of intestinal tract, no significant and dose-dependent reduction in intestinal tumor number or size was observed. But intestinal adenomas in *Min* mice were generated by a germline mutation in *Apc* gene rather than by chronic inflammation and it was not a colitis-associated colon cancer model^[23]. The author^[21] cautioned that their findings did not definitively exclude the possibility that 5-ASA might exert a chemopreventive effect on human IBD patients. Furthermore, their experimental results were not proved^[38]. MacGregor *et al* treated B6-*Min/+* mice by balsalazide from 55 d of age for 90 d and intestinal tumors were studied. In B6-*Min/+* mice a dose-dependent reduction of intestinal tumor number was observed, which reached 80% in the distal small intestine and colon.

The process of OH⁻-induced DNA modification involving 8-OH guanine, 8-adenine, and other hydroxylation products has been assumed to lead to carcinogenic mutations through transversions or transitions with consecutive misreplications in DNA polymerization, especially in genes important for growth regulation and cell differentiation^[42]. As increased quantities of 8-OH guanine and other hydroxylated DNA bases have been found in a variety of tumors of liver, pancreas,

breast or stomach, a variety of exogenous and endogenous factors, such as acute or chronic inflammation, may induce base hydroxylation. It was reported that increased quantities of hydroxylated DNA bases might play a role in colonic malignancies^[43]. This view is supported by the observation of increased quantities of 8-OH guanine and other hydroxylated products in IBD as the result of enhanced oxidative stress and decreased antioxidant defense^[44]. Allgayer *et al*^[45] found that 5-ASA concentration-dependently inhibited OH[•]-stimulated generation of hydroxylated DNA bases. The inhibition of OH[•]-stimulated base hydroxylation in DNA by 5-ASA, N-acetyl-ASA, and salicylate most likely is the result of direct interactions with OH[•] due to their oxygen radical scavenger properties, thus preventing base and DNA damage. Other authors reported that 5-ASA and 4-ASA had similar protecting effects on deoxyribose, another major DNA component, in the presence of OH[•] produced during the Fenton reaction. Allgayer *et al* observed an enhancement of OH[•]-stimulated base hydroxylation in DNA, especially 8-OH adenine, by bile acids at low (plasma) concentrations. On the other hand, 5-ASA and Na⁺-salicylate (the major aspirin metabolite), at concentrations that may be expected intraluminally in patients taking these drugs, inhibited this hydroxylation. The author deduced that these observations might be clinically relevant with the chemoprevention of colonic malignancy and the chemopreventive mechanisms of 5-ASA and Na⁺-salicylate could be mediated by preventing oxygen radical-induced DNA damage.

Safety of 5-ASA

Although 5-ASA is considered a safe drug in treatment of IBD and its adverse effects are relatively few^[28,29], a few earlier reports^[46,47] suggest that the potential toxicity of 5-ASA should be considered, in particular during long-term treatment with 5-ASA delivering compounds at doses more than 1 g/d. A side effect is the potential renal abnormalities due to 5-ASA. The drug has structural similarities to phenacetin, and leads to papillary necrosis when given intravenously at high doses to rats. A putative nephrotic syndrome and an interstitial nephritis after treatment with Asacol and Salofalk, respectively were reported^[48,49]. A two-year follow up of patients on Asacol has shown an incidence of pyuria of more than 50%. So the high concentrations of free 5-ASA in the intestinal lumen and the lowest possible systemic load of 5-ASA should be sought for effective delivery of 5-ASA to the inflamed colon^[28,50-53].

DISCUSSION

Prevention of colorectal cancer by administration of chemopreventive agents is one of the most promising options for IBD patients who are at increased risks of the disease^[54-57]. Successful implementations of chemoprevention depend not only on the accurate identification of high-risk population but also on the development of safe and effective drugs suitable for use in these specific populations. As chemoprevention of colorectal cancer must meet very high standards of safety and efficacy, 5-ASA has a well-established place in the management of patients suffering from IBD. Furthermore, high concentrations of this drug can be achieved in the colon lumen following oral and/or topical administration, which is another requirement of chemopreventive agent. So from the literature^[54-72], this agent might well satisfy clinical expectations with respect to a safe and effective chemopreventive agent. Randomized, well-designed, placebo-controlled prospective studies should be conducted in more IBD populations and further confirmative studies are needed in cell culture experiments, animal studies

and clinical trials to elucidate the exact mechanisms of 5-ASA in chemoprevention of colon cancer.

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