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Original Article

Chemopreventive effects of 5-amino salicylic acids on inflammatory bowel disease-associated colonic cancer and colonic dysplasia: a meta-analysis

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Abstract: Purpose: To study the effects of 5-amino salicylic acids (5-ASAs) on the incidence rates of inflammatory bowel disease (IBD)-associated colonic cancer (IBDACa) and colonic dysplasia (IBDADys), as well as to evaluate the chemopreventive effects of 5-ASAs on IBDACa/Dys. Methods: Searches for officially published clinical studies on the effects of 5-ASAs on the chemoprevention of IBDACa/Dys were conducted in both foreign-language databases, including PubMed (Medline), EMCC, OVID, and the Cochrane Library, and Chinese databases, including Wanfang, Weipu (VIP), and CNKI, as well as using Google Scholar. For literature matching the selection criteria, the statistical software RevMan was employed to calculate odds ratio (*OR*) values and 95% confidence intervals (CIs). Sub-group analysis was performed for different study design types and IBD types. Results: A total of fourteen papers were included in this study. The results of the analysis showed that compared with patients not using 5-ASAs, patients using 5-ASAs showed only 49% of the occurrence rate of IBDACa and IBDADys, *OR* = 0.49 (95% CI: 0.33-0.73). The *OR* of ulcerative colitis (UC) patients using 5-ASAs exhibiting UCCa/Dys was 0.44 (95% CI: 0.26-0.76). Conclusion: The use of 5-ASAs exerts a chemopreventive effect against IBDACa/Dys.

Keywords: 5-Amino salicylic acids, inflammatory bowel disease, ulcerative colitis, Crohn's disease, colon cancer, dysplasia, chemoprevention, meta-analysis

Introduction

Inflammatory bowel disease (IBD) primarily consists of ulcerative colitis (UC) and Crohn's disease (CD). IBD patients show significantly increased incidence rates of IBD-associated colonic cancer (IBDACa). IBDACa/Dys (IBD-associated colonic dysplasia (IBDADys) is an important cause of death in IBD patients. The occurrence of IBDACa/Dys is related to factors such as the extent of IBD disease, disease duration, degree of inflammatory response, age of onset, and a family history of colorectal cancer [1]. When the course of UC disease is longer, the risk of developing UCACa is higher. UC patients with a 10-year course display a cancer rate of 2%, patients with a 20-year course show a rate of 8%, and patients with a 30-year course exhibit a heightened cancer rate of 18% [2]. Although prophylactic colectomy can prevent the occurrence of IBDACa, this procedure significantly affects a patient's life quality, which is not easy to accept for both patients and doctors. Regular electronic colonoscopy is an important means of early diagnosis of IBDACa (considered secondary prevention) [3]. However, IBDACa usually shows a multicentric occurrence, and the follow-up time interval of colonoscopy is currently controversial, which results in a heavy economic burden and an emotional burden for patients [4]. Therefore, many researchers have been attempting to explore the treatment of IBD and, at the same time, to identify drugs with preventive effects against IBDACa in the hope that these drugs can prevent, inhibit or even reverse the occurrence and development of IBDACa. The drugs currently being evaluated include 5-amino salicylic acids (5-ASAs), folic acid, azathioprine, and mercaptopurine, among which 5-ASAs are the first-line drug

Table 1. The basic characteristics of the included studies

First author	Publication Year	Number of Subjects		OR/RR	95% CI	IBD type	5-ASA treatment		Outcomes
		IBDACa/Dys	Non-IBDACa/Dys				Categories	Definition*	
Pinczowski	1994	102	196	0.36	0.22-0.58	UC	SASP	Continuous ≥ 3 months	Ca
Eaden	2000	102	102	0.21	0.11-0.41	UC	SASP/Mesa	5 to 10 years (Interrupt < 1 year)	Ca
Bernstein	2003	25	348	1.46	0.64-3.36	UC/CD	-	Continuous ≥ 2 years	Ca
Rutter	2004	68	136	2.49	0.69-8.97	UC	SASP/non-SASP	> 3 years	Ca/Dys
van Staa	2005	100	600	0.67	0.44-1.03	UC/CD	SASP/Mesa/Balsa/Olsa	≥ 6 years	Ca
Rubin	2006	26	96	0.23	0.08-0.66	UC	SASP/Mesa/Olsa	> 1.2 g/d**	Ca/Dys
Velayos	2006	188	188	0.59	0.39-0.90	UC	SASP/Mesa/Balsa/Olsa	> 1 year	Ca
Siegel	2006	27	27	0.34	0.11-1.04	CD	-	> 1 year (Regular 5-ASA)	Ca
Terdiman	2007	364	1172	0.97	0.77-1.23	UC/CD	SASP/Mesa/Balsa/	used 1 year before diagnosis	Ca
Tang	2010	18	30	0.36	0.08-1.27	UC/CD	Mesa	> 1.6 g/d	Ca
Moody	1996	10	158	0.07	0.02-0.30	UC	SASP	Long-term (compliant)	Ca
Lasher	1997	29	69	0.20	0.02-2.28	UC	SASP/Mesa	≥ 6 months	Ca/Dys
Lindberg	2001	50	92	0.64	0.24-1.74	UC	SASP	≥ 6 months	Ca/Dys
Ullman	2008	17	294	0.49	0.14-1.73	UC	SASP/Mesa/Balsa/Olsa	> 2 g/d**	Ca/Dys

Note: SASP: sulfasalazine; Mesa: mesalazine; Balsa: Bechara triazine; Olsa: Olsalazine; Ca: cancer; Dys: intraepithelial neoplasia. *Defined based on original research, mainly based on 5-ASA treatment and dose. **A daily dosage of mesalamine, daily dosage of other drugs may be obtained through the conversion, namely, 1 g of sulfasalazine equals 0.4 g of mesalamine; 1 g of Olsalazine equals 1 g mesalazine.

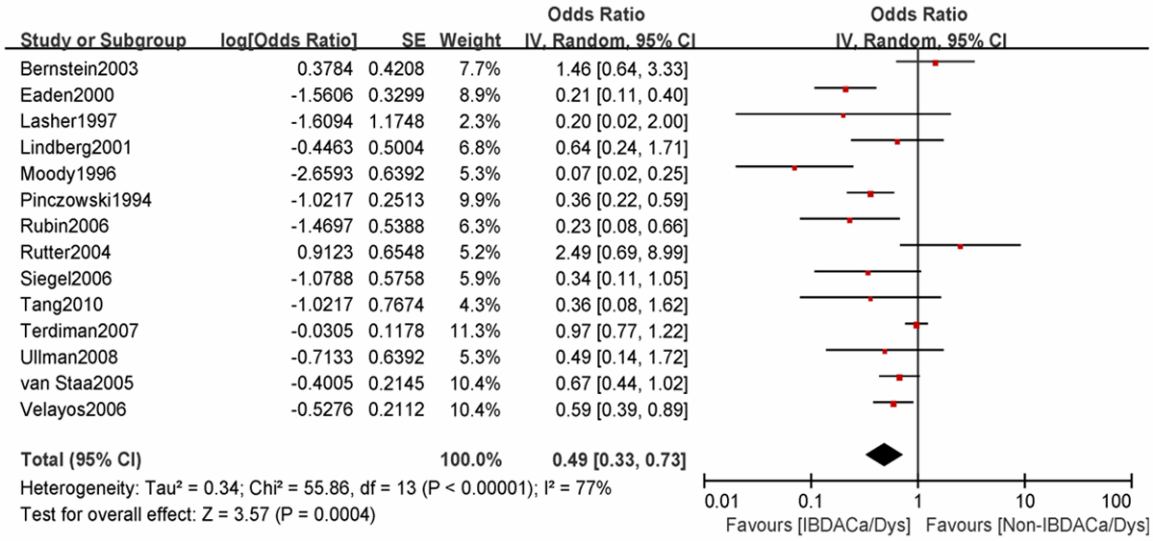

Figure 1. Forest plot of 5-ASA and IBDACa/Dys. The horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

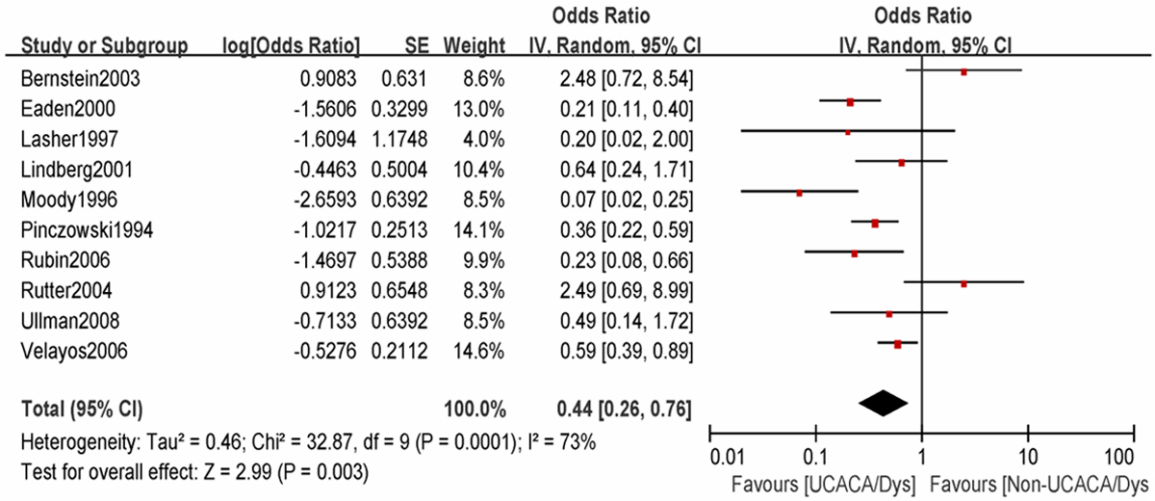

Figure 2. Forest plot of 5-ASA and UCACa/Dys. The horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

for the induction of IBD remission and the maintenance of remission. Many researchers are devoted to studying the chemopreventive effects of 5-ASAs on IBDACa/Dys. Studies have shown that 5-ASAs exert a chemopreventive effect against IBDACa [5-19]. However, the final conclusion regarding these effects remains controversial. In this study, we performed a meta-analysis of the effect of 5-ASAs on the incidence rates of IBDACa and IBDADys, providing information contributing to clinical decisions.

Materials and methods

Search strategies

Computer searches of the officially published literature on the chemopreventive effect of 5-ASAs against IBDACa/Dys were performed using foreign-language databases including PubMed (Medline), EMCC, the Cochrane Library, and OVID. The applied English search terms were as follows: 5-ASA, 5-aminosalicylate, 5-aminosalicylic acid, mesalamine, mesalazine,

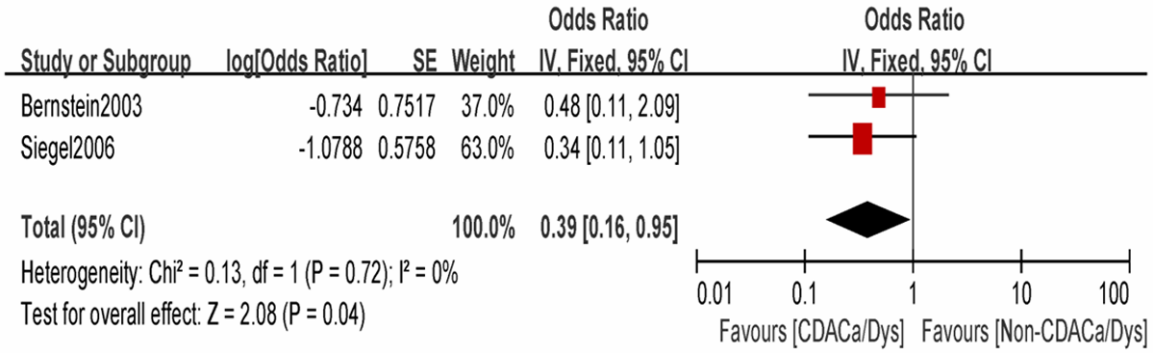

Figure 3. Forest plot of 5-ASA and CDACa/Dys. The horizontal lines correspond to the study-specific OR and 95% CI, respectively. The area of the squares reflects the study-specific weight. The diamond represents the pooled results of OR and 95% CI.

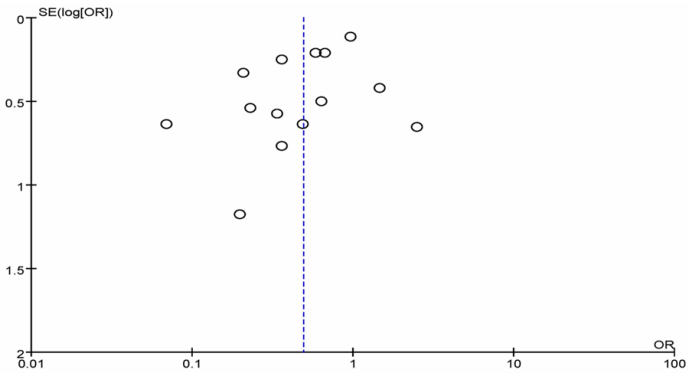

Figure 4. Begg's funnel plot for publication bias tests. Each point represents a separate study for the indicated association. Log or represents the natural logarithm of OR. The vertical line represents the mean effects size.

sulfasalazine, sulphasalazine, olsalazine, balsalazide, ulcerative colitis, Crohn's disease, inflammatory bowel disease, colorectal cancer, colonic cancer, dysplasia, neoplasia, and chemoprevention. Chinese databases, including Weipu, Wanfang, and CNKI, and Google Scholar searches were also used. In addition, relevant literature was searched based on references.

Literature selection

The selection of studies was performed based on the literature searches. The inclusion criteria were as follows: (1) the definition of 5-ASA usage in IBD patients was clarified (5-ASAs include one or multiple types of sulfasalazine, balsalazide, mesalazine and olsalazine); (2) raw data from a case group and a control group using 5-ASAs (or raw data on IBDACa/Dys occurrence in an exposure group and a non-exposure group) were reported; and (3) a diagnosis of IBDACa/Dyso was clearly established. The following exclusion criteria were applied: (1) cell studies and animal experiments; (2) reviews and letters; and (3) repeated reports from the same study group.

Quality evaluation and information extraction

The Lichtenstein standard [21] was used to evaluate the cohort studies and case-control studies, including their research question statements; source of cases and the applied diagnostic methods; source of controls and the applied diagnostic methods, including whether they were consistent with the cases; detailed definition of 5-ASA usage (detailed dosage and usage duration); and description of data collection methods, analysis methods, and sample sizes.

Information was extracted from the literature retained for the analysis, including the authors, years, study design types, study times, IBD types, original definition of 5-ASA usage (including drug types, treatment duration, drug usage method, and dosage), result types (cancer or dysplasia), and number of cases in the study group and control group.

Statistical analysis

RevMan 5.2 software provided by the Cochrane Collaboration website was used to analyze of the results. Because IBDACa/Dys is relatively rare, we employed odds ratio (*OR*) values to evaluate the relative risk (*RR*). First, a test of

heterogeneity was performed, in which P > 0.10 indicated homogeneity. A fixed effects model was used to calculate *OR* values and 95% CIs; P < 0.10 indicated heterogeneity (or non-homogeneity), in which case a random effects model was used to calculate the *OR* value and 95% CI. A funnel plot was drawn using the *OR* value as the abscissa and the log (*OR*) standard error (SE (log [*OR*])) as the ordinate to evaluate the publication bias.

Results

Basic characteristics of the included studies

Based on the adopted search strategy, both electronic searches and manual searches were performed. Based on reviewing the abstracts, the publications were screened according to the inclusion and exclusion criteria. Subsequently, a quality evaluation of the included literature was performed, and a total of 14 papers meeting the criteria were finally selected (**Table 1**).

Meta-analyses

The results of the heterogeneity test were as follows: P < 0.00001; I^2 = 77%, indicating non-homogeneity. As a random effects model, the Mantel-Haenszel method was used for analysis, and the results showed that the occurrence of IBDACa/Dys in IBD patients with 5-ASA usage presented an *OR* of 0.49 (95% CI; 0.33~0.73) (**Figure 1**).

A stratified analysis was performed based on the effect of 5-ASAs on UC and CD. The results of the heterogeneity analysis of the effect of 5-ASAs on UC were as follows: P < 0.001, I^2 = 73%, indicating non-homogeneity. As a random effects model, Mantel-Haenszel analysis indicated an *OR* of the occurrence of UCACa/Dys in UC patients using 5-ASAs of 0.44 (95% CI: 0.26-0.76, **Figure 2**). The results of the heterogeneity analysis of the effect of 5-ASAs on CD were as follows: P > 0.10, I^2 = 0%, indicating homogeneity. As a fixed effects model, the Mantel-Haenszel method was used for analysis, and the results indicated an *OR* of CDACa/Dys occurrence in CD patients using 5-ASAs of 0.39 (95% CI: 0.16-0.95, **Figure 3**).

Publication bias

Funnel plots for the included studies basically resulted in a symmetric graph. Therefore, the publication bias is low (**Figure 4**).

Discussion

In this study, we performed a meta-analysis of the effect of 5-ASAs on the incidence rate of IBDACa/Dys, with the aim of investigating the chemopreventive effects of 5-ASAs on IBDACa/Dys. We strictly followed the inclusion and exclusion criteria to screen the literature and performed a quality evaluation of the included publications. A total of 14 papers meeting the criteria were included. The meta-analysis results revealed *OR* values for IBDACa/Dys, UCACa/Dys, and CDACa/Dys occurrence in IBD patients, UC patients, and CD patients using 5-ASAs of 0.49 (95% CI: 0.33-0.73), 0.44 (95% CI: 0.26-0.76), and 0.39 (95% CI: 0.16-0.95), respectively, suggesting that 5-ASAs exert a chemopreventive effect against IBDACa/Dys.

In a broad sense, 5-ASA preparations primarily include balsalazide, SASP, mesalazine and olsalazine. Among these agents, balsalazide and SASP are prodrugs of 5-ASA, and both of them release 5-ASA under the action of colonic bacteria; mesalazine is a controlled-release form of 5-ASA; and olsalazine is a 5-ASA dimer. The active components of these agents are all 5-ASAs, and they are used as first-line drugs for inducing the remission of mild-moderate UC and for maintaining remission. Good tolerance, few side effects, and definite anti-inflammatory effects are observed for 5-ASAs. However, animal experiments did not show a good preventative effect of 5-ASAs against colorectal cancer [22]. Additionally, researchers found that after IBD patients had used 5-ASAs or SASP for 6 months [18], 12 months [15], or 24 months [9], the incidence of colon cancer did not show a significant difference compared with IBD patients not using 5-ASAs or SASP. Ullman et al. [20] studied the occurrence of severe dysplasia and UCACa in UC patients without dysplasia, with uncertain dysplasia and with mild dysplasia after they had used 5-ASAs. Their results suggested that mesalazine (either with a dosage > 2 g/d or ≤ 2 g/d) had no effect on UCACa occurrence. Therefore, the above studies showed that different treatment durations as well as different dosages of 5-ASAs show no significant effect on the occurrence of UCACa, *i.e.,* that 5-ASAs exhibit no definite chemopreventive effect on UCACa. However, there are also numerous studies suggesting that 5-ASAs display a definite chemopreventive effect against UCACa [8, 11, 12, 16, 17, 23]. For example, cell

biology studies and animal experiments demonstrated that mesalazine can inhibit the growth of various colon cancer cell lines, including the wild-type p53 HCT116 and mutant p53HT-29 and Caco-2 colon cancer cell lines [24, 25], as well as significantly decreasing the azoxymethane/dextran sodium sulfate (AOM/DSS)-induced occurrence of UCACa in mice [26]. Clinical cohort studies also suggested that UC patients with long-term use of sulfasalazine exhibit a significantly decreased UCACa incidence rate [17]. Furthermore, case-control studies suggested that treatment with regular doses of 5-ASAs can significantly decrease the UCACa incidence rate (OR = 0.19) [8, 16].

The differences in the conclusions of the above studies may be related to the genetic background, IBD disease duration, or duration and dosage of 5-ASA treatment among the examined IBD patients. In the above studies, the sources of IBD patients were inconsistent. For example, the evaluated UC patients came from Europe, Asia, and other areas with different environments and showed different genetic backgrounds. Additionally, there is no uniform standard for the detailed definition of 5-ASA usage, and there may be differences in 5-ASA types, usage times, or dosages. All of these factors could cause inconsistent study results. Therefore, a meta-analysis of the relationship between 5-ASAs and IBDACa/Dys has value in relation to providing clinical guidance. Our meta-analysis results suggested that 5-ASAs exert a chemopreventive effect on the occurrence of IBDACa/Dy in IBD patients overall and in UC or CD patients.

However, our meta-analysis has the following limitations: (1) it lacks randomized control trials (RCTs); (2) the included publications are not of a single type (both case-control and cohort studies), which may affect the quality of the meta-analysis; and (3) the definitions of 5-ASA usage are different in the included publications, with some being defined based on the treatment duration, while others are defined based on dosage. Therefore, it is difficult to determine the best values for the duration and dosage of 5-ASA treatment to provide best-usage recommendations for clinics. Therefore, more rigorously designed, high-quality, randomized controlled trials (RCTs) and biological studies addressing drugs such as 5-ASAs should be performed to provide more definitive and precise evidence of chemoprevention for translation to clinical practice.

Disclosure of conflict of interest

None.

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