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## Characteristics and therapeutic efficacy of sulfasalazine in patients with mildly and moderately active ulcerative colitis

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### Abstract

**AIM:** To investigate the characteristics and short-term efficacy of sulfasalazine (SASP) in patients with mildly and moderately active ulcerative colitis (UC).

**METHODS:** Two hundred and twenty-eight patients with mildly and moderately active UC were recruited, 106 patients in 1993-1995, and 122 patients in 2000-2002, they were assigned as the 1990s group ( $n = 106$ ) and the 2000s group ( $n = 122$ ), prospectively. The general characteristics, clinical manifestations, colonoscopic and histological data were compared between the two groups. The short-term efficacy and safety of SASP 3 g per d were evaluated.

**RESULTS:** Between 2000s and 1990s groups, the gender ratio of men to women was 1:1.18 and 1:1.04, 57.4% and 50.9% of the patients were between 30 and 49 years old. The gender ratio and age of UC patients were not significantly different. The total course of 50.0% and 37.1% of UC patients was less than 1 year ( $P < 0.05$ ), 10.6% and 31.2% of the cases had a duration of more than 5 years ( $P < 0.05$ ) in 2000s and 1990s groups, respectively. The

most common clinical type was first episode in 2000s group and chronic relapse in 1990s group. The patients showed a higher frequency of abdominal pain and tenderness in 1990s group than in 2000s group. Erosions were found in 84.4% and 67.9% of patients in 2000s and 1990s groups ( $P < 0.05$ ). Rough and granular mucosa (67.9% vs 43.4%,  $P < 0.05$ ) and polyps (47.2% vs 32.8%,  $P < 0.05$ ) were identified in 1990s group more than in 2000s group. There were no significant differences in clinical, colonoscopic and histological classifications. After SASP (1 g thrice per d) treatment for 6 wk, the clinical, colonoscopic and histological remission rates were 71.8%, 21.8% and 16.4%, respectively. In 79 patients with clinical remission, 58.2% and 67.1% remained grade 1 in colonoscopic and histological findings, respectively. The overall effects in first episode type (complete remission in 10, 18.9%, partial remission in 28, 52.8%, and improvement in 9, 17.0%) were better than in chronic relapse type (complete remission in 3, 7.5%; partial remission in 16, 40.0%; and improvement in 15, 37.5%) and chronic persistent type (complete remission in 1, 5.9%; partial remission in 6, 35.3%; and improvement in 6, 35.3%) respectively ( $P < 0.05$ ). In 110 patients treated with SASP, 18 patients (16.4%) had adverse reactions. Except for two cases of urticaria and one case of WBC decrease, none of the patients had to stop the treatment because of severe adverse reactions.

**CONCLUSION:** Patients with mildly and moderately active UC in 2000s group had a shorter disease course, milder clinical manifestations, more first episode type and higher frequency of acute mucosal lesions in colonoscopy than in 1990s group. The patients in 1990s group had higher proportion of chronic relapse type and chronic mucosal change in colonoscopy than in 2000s group. The short-term efficacy of SASP could be mainly remission of clinical manifestations. But more than half of the patients still had light inflammation in colonoscopy and histology. The overall effects of SASP in first episode type were better than those in other types. SASP was a safe and effective drug to treat mildly and moderately active UC.

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**Key words:** Sulfasalazine; Ulcerative colitis; Pharmacodynamics

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## INTRODUCTION

Ulcerative colitis (UC) is a common disease in countries of Northern America and Europe. The incidence and modality of UC might vary greatly across the world<sup>[1-7]</sup>. China is an area with relatively low incidence of UC. With the changes of lifestyle and environmental factors, patients with UC have increased persistently and UC has become one of the most common causes of chronic diarrhea. The aim of this study was to compare the differences of the general characteristics, clinical manifestations, colonoscopic and histological involvements between patients in 1993-1995 and in 2000-2002, and investigate short-term efficacy and safety of sulfasalazine (SASP) in patients with mildly and moderately active UC.

## MATERIALS AND METHODS

### Patients

Two hundred and twenty-eight patients with mildly and moderately active UC were collected according to the criteria of diagnosis and treatment issued by National Symposium of Chronic and Non-infectious Intestinal Diseases of Taiyuan in 1993<sup>[8]</sup>. All patients were diagnosed with colonoscopy. There were 108 male patients and 120 female patients. The mean age was  $41.3 \pm 12.4$  years (range 18-65 years).

### Methods

The data of 228 patients were collected in The Second and First Affiliated Hospital of Sun Yat-Sen University; The First People's Hospital of Guangzhou City; Peking Union Medical College Hospital; First and Third Hospital of Peking University and Beijing Friendship Hospital of Capital University of Medical Science. One hundred and six patients were from 1993-1995, and 122 patients from 2000-2002, they were assigned as the 1990s group and the 2000s group, respectively. The general characteristics, clinical manifestations, laboratory results, colonoscopic and histological involvements were compared between the two groups. The stool bacterial culture and amebic examination were carried out for 3 d continuously to exclude bacterial and amebic infection. The patients had not received any medical treatment for UC 1 mo prior to enrollment.

The activity index (AI) of the diseases was quantified by the scoring system of Seo<sup>[9,10]</sup>:  $AI = 60X_1 + 13X_2 + 0.5X_3 - 0.4X_4 - 1.5X_5 + 200$ . In this system,  $X_1$  = the extent of bloody stools ( $X_1 = 0$ , no bloody stool;  $X_1 = 1$ , obvious bloody stool),  $X_2$  = times of stool per day,  $X_3$  = ESK,  $X_4$  = hemoglobin,  $X_5$  = serum albumin. AI values below 150, values between 150 and 220, and values above 220 corresponded to grades 1-3 of clinical classification. The colonoscopic classification was graded according to the criteria by Baron<sup>[11]</sup>. In this system, 0 = normal mucosa, 1 = congestive edema and loss of vascular pattern of mucosa, 2 = mucosal friability and bleeding contacted, 3 = mucosal bleeding spontaneously, 4 = mucosal ulceration. The pathological diagnosis and classification were scored according to the criteria by Truelove and Richards<sup>[12]</sup>: 0 = no neutrophil infiltration in the lamina propria of mucosa, 1 = neutrophil infiltration ( $<10$ /HP), 2 = neutrophil infiltration (10-50/HP) with more than 50% of crypt involved, 3 = neutrophil infiltration

( $>50$ /HP) with crypt abscesses, 4 = acute inflammation and ulceration.

### Therapeutic protocol

One hundred and ten patients were included in the therapeutic protocol of SASP (1 g, thrice a day) for 6 wk. The clinical types of 110 patients were first episode ( $n = 53$ ), chronic relapse ( $n = 40$ ) and chronic persistent ( $n = 17$ ). Fifty-three patients were in 1990s group and 57 patients in 2000s group, respectively. The clinical remission meant the absence of clinical manifestations, less than twice of soft and shaped stool per day normalization of hemoglobin, ESR and serum albumin. The overall effects of UC patients treated with SASP were evaluated according to complete remission, partial remission, improvement and inefficiency. Complete remission meant that clinical and colonoscopic classifications became grade 0 and that histological classification was not more than 1 score. Partial remission showed that clinical classification was grade 0 and that colonoscopic and histological classifications were improved more than 1 score. Improvement meant that one of clinical or colonoscopic or histological classification was improved more than 1 score. Adverse reactions were recorded simultaneously.

### Statistical analysis

All data were analyzed with SPSS 10.0/PC statistical package. The frequency was compared by the  $\chi^2$  test. The rank data were compared with Ridit test.

## RESULTS

### Patients' characteristics

Among 228 patients with mildly and moderately active UC, the gender ratio (M/F) was 1:1.18 and 1:1.04 in 2000s and 1990s groups ( $P > 0.05$ ), respectively. The distribution of age, course of the illness and clinical types of mildly and moderately active UC are shown in Tables 1 and 2.

**Table 1** Distribution of age and course of the illness

Age and course		2000s group <i>n</i> (%)	1990s group <i>n</i> (%)
Age (yr)	<30	21 (17.2)	19 (17.9)
	30-	31 (25.4)	33 (31.1)
	40-	39 (32.0)	21 (19.8)
	50-	14 (11.5)	21 (19.8)
	60-	17 (13.9)	12 (11.3)
Total course of the illness (yr)	<1.0	61 (50.0) <sup>a</sup>	33 (31.7)
	1.0-	48 (39.3)	40 (37.7)
	5.0-	6 (4.9) <sup>a</sup>	18 (17.0)
	10.0-	7 (5.7) <sup>a</sup>	15 (17.0)
Course of present flare-up (yr)	<0.5	85 (69.7)	71 (67.0)
	0.5-	20 (16.4)	17 (16.0)
	1.0-	17 (13.9)	18 (17.0)

<sup>a</sup> $P < 0.05$  vs 1990s group.

### Clinical manifestations

The major clinical manifestations were abdominal discomfort

(59.8% *vs* 69.8,  $P>0.05$ ), abdominal pain (57.4% *vs* 71.2%,  $P<0.05$ ), tenesmus (40.0% *vs* 50.0%,  $P>0.05$ ), abdominal tenderness (32.8% *vs* 46.2%,  $P<0.05$ ), abdominal distention (28.7% *vs* 31.1%,  $P>0.05$ ) between patients in 2000s and 1990s group. The changes of stool frequency and property are shown in Table 3.

**Table 2** Clinical types of the illness

Type of the illness	2000s group <i>n</i> (%)	1990s group <i>n</i> (%)
First episode	62 (50.8) <sup>a</sup>	37 (34.9)
Chronic relapse	38 (31.0) <sup>a</sup>	60 (56.6)
Chronic persistent	22 (18.1)	9 (8.5)

<sup>a</sup> $P<0.05$  *vs* 1990s group.

**Table 3** Frequency and property of stool

Frequency of stool and property	2000s group <i>n</i> (%)	1990s group <i>n</i> (%)
Frequency of stool		
<21	53 (43.4)	40 (37.7)
(times per week)		
21-	57 (46.2)	48 (45.5)
42-	12 (9.8)	18 (17)
Property of stool		
Nonmucous	36 (29.5)	27 (25.5)
and bloody stool		
Slight mucous	43 (35.2)	30 (28.3)
and bloody stool		
Slight mucous	43 (35.2)	49 (46.2)
and bloody stool		

### Colonoscopic findings

The types of lesions of the patients included proctitis (29.5% *vs* 21.7%,  $P>0.05$ ), left-sided colitis (48.4% *vs* 61.3%,  $P>0.05$ ), extensive colitis (18.9% *vs* 17.0%,  $P>0.05$ ) and local colitis (3.3% *vs* 0%,  $P>0.05$ ) in 2000s group and 1990s group, respectively. The colonoscopic findings were congestive edema (98.4% *vs* 98.1%,  $P>0.05$ ), erosion (84.4% *vs* 67.9%,  $P<0.05$ ), mucosal friability and bleeding contacted (90.2% *vs* 88.7%,  $P>0.05$ ), rough and granular mucosa (43.4% *vs* 67.9%,  $P<0.05$ ), ulceration (59.8% *vs* 48.1%,  $P>0.05$ ), purulent secretion (20.5% *vs* 27.4%,  $P>0.05$ ), spontaneous bleeding (72.1% *vs* 83%,  $P>0.05$ ) and polyps (32.8% *vs* 47.2%,  $P<0.05$ ) in 2000s group and 1990s group, respectively.

### Clinical, colonoscopic and histological classifications

Clinical, colonoscopic and histological classifications at diagnosis are shown in Table 4. There were no significant differences in classifications between 2000s and 1990s groups.

**Table 4** Clinical, colonoscopic and histological classifications

Classifications	Clinical <i>n</i> (%)		Colonoscopic <i>n</i> (%)		Histological <i>n</i> (%)	
	2000s group	1990s group	1990s group	2000s group	2000s group	1990s group
Grade 1	64 (52.5)	41 (38.7)	25 (20.5)	10 (9.4)	25 (20.5)	14 (13.3)
Grade 2	53 (43.4)	57 (53.8)	46 (37.7)	36 (34.0)	46 (37.7)	33 (31.1)
Grade 3	5 (4.1)	8 (7.5)	37 (30.3)	11 (10.4)	39 (32.1)	40 (37.7)
Grade 4			14 (11.5)	49 (46.2)	12 (9.8)	19 (17)

### Comparison of clinical, colonoscopic and histological classifications before and after treatment with SASP

The short-term efficacy of SASP in 110 patients with mildly and moderately active UC is shown in Table 5. In 79 patients of clinical remission, only 21 (26.6%) and 14 (17.7%) of cases were grade 0, most of the patients (58.2% and 67.1%) remained grade 1 by colonoscopic and histological examination.

**Table 5** Comparison of clinical, colonoscopic and histological classifications before and after treatment with SASP in 110 patients

Classification	Clinical <i>n</i> (%)		Colonoscopic <i>n</i> (%)		Histological <i>n</i> (%)	
	Before	After	Before	After	Before	After
Grade 0	0	79 (71.8)	0	24 (21.8)	0	18 (16.4)
Grade 1	56 (50.9)	27 (24.6)	7 (6.4)	56 (50.9)	21 (19.1)	67 (60.9)
Grade $\geq 2$	54 (49.1)	4 (3.6)	103 (93.6)	30 (27.3)	89 (80.9)	25 (22.7)
<i>P</i>	<0.01		<0.01		<0.01	

### Comparison of efficacy between UC patients with different types of the illness treated with SASP

The comparison of efficacy between the patients with different types of the illness treated with SASP is shown in Table 6. There were significant differences among first episode, chronic relapse and chronic persistent types ( $P<0.01$ ).

**Table 6** Comparison of efficacy in the patients with different types of the illness treated with SASP

The overall effects	First episode <i>n</i> (%)	Chronic relapse <i>n</i> (%)	Chronic persistent <i>n</i> (%)
Complete remission	10 (18.9)	3 (7.5)	1 (5.9)
Partial remission	28 (52.8)	16 (40.0)	6 (35.3)
Improvement	9 (17.0)	15 (37.5)	6 (35.3)
Inefficiency	6 (11.3)	6 (15.0)	4 (23.5)
<i>P</i>	<0.05		

### Adverse reactions of SASP

In 110 patients treated with SASP, 18 of them (16.4%) had one or more than one kind of adverse reactions: two patients had urticaria, three fever, five dizziness, four nausea, six anorexia, one fatigue, one WBC decrease, four AST increase and three ALT increase. Except for the cases with urticaria and WBC decrease, none of the patients had to stop the treatment because of severe adverse reactions.

## DISCUSSION

UC is a chronic inflammatory bowel disease (IBD) of unknown etiology. In European countries, the overall incidence was 10.4 per 100 000 between ages 15 and 64 years old<sup>[13]</sup>. UC was found mainly in male patients at ages of 25-34 years. The number of UC patients doubled every 10 years in countries of high prevalence. The incidence of UC may vary greatly across world<sup>[1,2,13,14]</sup>. The epidemiological investigation based on population was not reported in China. But the cases of UC reported were greatly increased over the last 10 years<sup>[15]</sup>. UC has become one common cause of

chronic diarrhea in China.

Although an accurate diagnosis of IBD and differentiation between UC and Crohn's disease are sometimes difficult even after thorough pathological study, severe UC is diagnosed easily<sup>[16]</sup>. Mildly and moderately active UC are difficult to identify because of non-specific clinical and colonoscopic findings. Varied geographical, climate, social, environmental, psychological and genetic factors may affect the incidence of UC<sup>[17-21]</sup>. China, a geographical area with the characteristics of the sub-tropics, has a lower prevalence of UC. There are few data on mildly and moderately active UC.

In this study, the gender ratio (M/F) was smaller in 2000s group than in 1990s group, but there was no significant difference. The peak age range was 30-49 years old, accounting for with 57.4% and 50.9% of the patients in 2000s group and 1990s group, respectively. It suggested that the susceptible populations could be middle-aged women. The total course of 50.0% and 37.1% of the patients was less than 1 year in 2000s group and 1990s group, but the total course of 10.6% and 37.1% of the patients was more than 5 years in 2000s group and 1990s group. There were more patients with abdominal pain and tenderness in 1990s group than in 2000s group. It suggested that the total course of UC might be shorter and that the extent of disease was lighter in 2000s group than in 1990s group. The clinical type of UC was mainly first episode in 2000s group and chronic relapse in 1990s group. It showed that UC patients were diagnosed earlier in recent years.

The patients with less than 21 times of stool per week accounted for 43.4% and 37.7%, but more patients (70.4% and 73.6%) were found to have bloody stool in 2000s group and 1990s group. The low frequent and mucous and bloody stool was characteristic of diarrhea of the patients with mildly and moderately active UC in this study. In clinical, colonoscopic and histological classifications, no significant differences were found in patients between 2000s and 1990s group.

Colonoscopic distribution of lesions in 2000s and 1990s group showed that 77.9% and 83.0% were found in leftside colon, and extensive colitis was found in 18.9% and 17.0% of the patients. Although mucosal edema and loss of vascular pattern were the most common colonoscopic findings, they had limited diagnostic values<sup>[22,23]</sup>. The frequency of mucosal erosions in 2000s group was higher than in 1990s group. However, more mucosal granularity and polyps were found in 1990s group than in 2000s group. The mucosal granularity and polyps were helpful to diagnose chronic relapse of UC. It showed that the patients had a higher proportion of chronic change in 1990s group than in 2000s group, and that the patients had a higher frequency of acute lesions in 2000s group than in 1990s group.

SASP is one of classic and commonly used medicine in treatment of mildly and moderately active UC<sup>[24,25]</sup>. In this study, short-term efficacy of SASP on mildly and moderately active UC showed obvious improvement of clinical manifestations, and relatively low remission of colonoscopic appearances and histological involvements. Light inflammatory changes were found in most of the patients, which corresponded to researches before. Therefore, the therapy of mildly and

moderately active UC with SASP as with 5-aminosalicylic acid needs a long course<sup>[26-29]</sup>.

Study showed that the overall effects of SASP on mildly and moderately active UC depended upon different clinical types of the illness. The overall effects of SASP in first episode type were better than those in chronic relapse type and in chronic persistent type. Because of its short-term efficacy, safety and inexpensiveness, SASP still is one of the common drugs for treatment of mildly and moderately active UC in China.

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