

# Usefulness of sulfasalazine for patients with refractory-ulcerative colitis

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## ABSTRACT

**Background:** Patients with refractory-ulcerative colitis (UC) require therapy escalation. Sulfasalazine (SASP) could deliver a high concentration of 5-aminosalicylic acid to the colon. The usefulness of SASP for refractory-UC patients, however, is unclear.

**Aim:** The aim was to evaluate the usefulness of SASP for refractory-UC patients.

**Method:** We retrospectively analysed 36 (11.4%) of 316 patients with refractory-UC who had been treated with SASP. Clinical and endoscopic activities were evaluated with Lichtiger index and Mayo score, respectively. We analysed the induction-remission rate, predictive factors for the efficacy of SASP, and adverse events.

**Results:** Of 36 refractory-UC patients, 14 (38.9%) were treated with concomitant mesalazine enemas, 10 (27.8%) with azathiopurine, 4 (11.1%) with tacrolimus and 6 (16.7%) with an antitumour necrosis factor- $\alpha$  agent. After initiating SASP treatment, 25 patients (69.4%) achieved clinical remission. In 9 (64.3%) of 14 patients with UC treated with mesalazine enemas, mesalazine enemas could be discontinued with SASP. In all patients treated with tacrolimus, tacrolimus could be discontinued with SASP. Clinical activity score upon the initiation of SASP was significantly lower ( $p=0.024$ ) and the number of patients treated with thiopurine was significantly higher ( $p=0.016$ ) in the clinical remission group than in the non-clinical remission group. These factors might be predictive for the efficacy of SASP, although multivariate analysis demonstrated no statistically significant effect. Adverse events occurred in 7 patients (19.4%), and reduction or discontinuation of SASP led to improvement.

**Conclusions:** SASP appears to be more effective for refractory-UC patients with low clinical-activity and/or thiopurine-use.

**Trial registration number:** UMIN000021615; Results.

## INTRODUCTION

Ulcerative colitis (UC) is a chronic-relapsing inflammatory colonic disorder.<sup>1</sup> Although recent basic studies demonstrated several factors involved in the pathophysiology of UC, such as environmental, genetic, immunological and microbial factors, the pathophysiology of UC has not been elucidated.<sup>2</sup> Despite the development of new

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## Summary box

### What is already known about this subject?

- ▶ Mesalazine is the mainstay for treatment of ulcerative colitis (UC).
- ▶ Sulfasalazine could deliver a high concentration of 5-aminosalicylic acid to the colon compared with that of controlled-release mesalazine agents.
- ▶ However, sulfasalazine could have more serious adverse events than for controlled-release mesalazine agents.

### What are the new findings?

- ▶ Treatment with sulfasalazine could induce clinical remission even in refractory-UC patients.
- ▶ Sulfasalazine treatment could contribute to discontinuing combination therapy, such as mesalazine enema and concomitant tacrolimus in our study.
- ▶ Sulfasalazine would be much more suitable for UC patients with low clinical activity and/or thiopurine use.

### How might it impact on clinical practice in the foreseeable future?

- ▶ In the era of biologics, our data reaware the usefulness of sulfasalazine for induction of remission in patients with low clinical activity and/or thiopurine-use resulting in discontinuing combination therapy and avoiding excessive therapy escalation.

agents for UC based on basic research, such as anti-tumor necrosis factor (TNF)- $\alpha$  agents, calcineurin inhibitors and  $\alpha 4\beta 7$  integrin inhibitors, a promising therapeutic strategy has not yet been established.<sup>3-6</sup> Developing and evaluating the efficacy of new agents is important, but is associated with several problems, such as safety concerns and economic load for patients due to high medical costs.<sup>7-9</sup> Therefore, re-evaluation and optimisation of conventional therapies for UC should be considered.

The mainstay of treatment for inducing and maintaining remission in patients with UC is 5-aminosalicylate (ASA)-based medications, particularly mesalazine.<sup>10</sup> A number of studies have demonstrated the efficacy of

controlled-release mesalazine for inducing and maintaining remission in patients with mildly to moderately active UC.<sup>11–14</sup> Patients with UC who are refractory to mesalazine often require therapy escalation, such as granulocyte monocyte adsorption apheresis (GMAA) and corticosteroids.<sup>15–16</sup> On the other hand, therapy escalation, particularly corticosteroid use, could be related with the induction of UC refractoriness, such as corticosteroid resistance and dependence.<sup>17–18</sup> To avoid therapy escalation, optimising treatment with 5-ASA is therefore important. Sulfasalazine (SASP), which is a combination of 5-ASA azo-bound to the antibiotic sulfapyridine, is effective for treating UC.<sup>19–22</sup> Systemic absorption of sulfapyridine, however, is associated with a high rate of adverse events, such as headache, skin rash, hepatic disorder, folate deficiency and male infertility.<sup>23–24</sup> Although more serious adverse events are reported for SASP than for controlled-release mesalazine agents, SASP delivers a high concentration of 5-ASA to the colon, which could contribute to better clinical outcome in patients with UC.<sup>25–27</sup> Therefore, SASP might be effective for patients with UC refractory to controlled-release mesalazine, allowing them to avoid therapy escalation. This study aimed to evaluate the usefulness of SASP for refractory-UC patients and the clinical factors associated with the efficacy of SASP to identify those patients most likely to benefit from SASP.

## METHODS

### Patients

From April 2010 to August 2015, 316 patients with UC treated at Kitano hospital were retrospectively analysed. The diagnosis of UC was confirmed by endoscopic and pathologic findings. We defined eligible patients for our study as those diagnosed with active UC based on endoscopic examination despite oral administration of more than 4 g of sustained-release mesalazine or 3.6 g of delayed-release mesalazine for two or more consecutive weeks, that had clinical symptoms relevant to UC with a clinical activity score greater than 5 points. UC patients treated concomitantly with a 1 g mesalazine enema were also included in the study. Moreover, UC patients treated with mesalazine who obtained a clinical response but had sustained-active UC after concomitant treatment with thiopurine, GMAA, tacrolimus, or an anti TNF- $\alpha$  agent, were enrolled in the study. All UC patients enrolled in the study were considered to have so-called refractory UC. Exclusion criteria included fulminant UC requiring urgent surgery, Crohn's disease, inflammatory bowel disease unclassified, and infectious or ischemic colitis. Of the 316 patients with UC, 36 (11.4%) with refractory-UC who were treated with SASP were enrolled in the study. This retrospective, observational, single-centre study was conducted according to the principles of the Declaration of Helsinki, and was reviewed and

approved by the Institutional Review Board at Kitano Hospital (P16-04-003, UMIN000021615).

### Treatment

For patients with refractory-UC, treatment with SASP was initiated. Based on patient's characteristics and the physician's decision, controlled-release mesalazine was changed to SASP at a dose of 4 g/day in 25 patients with UC. In the remaining 11 patients with UC, SASP at a dose of 1–2 g/day was added to the controlled-release mesalazine therapy.

### Evaluation of disease activity of UC

Clinical and endoscopic activities were evaluated according to the Lichtiger index and Mayo score, respectively.<sup>28–29</sup> Clinical remission was defined as a Lichtiger index of <4 under corticosteroid-free and GMAA-free conditions. Relapse of UC was defined as any recurrence of UC-related symptoms that required additional treatments.<sup>30</sup>

### Assessment and statistics

The primary outcome was the induction-remission rate of patients with UC refractory to mesalazine after initiating treatment with SASP. The secondary outcome included discontinuing combination therapy, identifying clinical factors associated with SASP efficacy and reporting adverse events related to SASP. Categorical and continuous data were compared using a two-tailed Fisher's exact test, Wilcoxon t-test or Mann-Whitney U test. To perform multivariate analysis to identify the clinical factors associated with SASP efficacy, the clinical factors suggested by the univariate analysis to be associated with SASP efficacy were analyzed by Cox regression. A p value of <0.05 was considered statistically significant.

## RESULTS

### Patient's characteristics

The characteristics of the 36 patients with UC refractory to mesalazine are shown in [table 1](#). Of the 36 patients, 27 (75.0%) were men and 9 (25.0%) were women. Median age was 41 years (range 18–85 years), and median disease duration was 2.0 years (range 0–20.3 years). The UC type was extensive colitis type in 21 (58.3%), left-sided type in 13 (36.1%) and proctitis type in 2 (5.6%). UC patients enrolled in this study were divided into four groups according to the clinical course, as previous reported,<sup>31</sup> initial attack type (n=8, 22.2%), chronic active type (n=13, 36.1%), chronic intermittent type (n=11, 30.6%) and acute severe type (n=4, 11.1%). Upon initiation of SASP treatment, the median clinical activity score and endoscopic Mayo score of the 36 patients with UC were 6 (range 5–16) and 2 (range 2–3), respectively. The median serum level of C-

**Table 1** Patient's characteristics

		n=36
Gender (M/F)		27/9
Age (year) (Median)		41 (18-85)
Disease Duration (year) (Median)		2.0 (0-20.3)
Extent of Disease (%)	Extensive colitis	21 (58.3)
	Left-sided type	13 (36.1)
	Proctitis	2 (5.6)
Clinical Course (%)	Initial attack type	8 (22.2)
	Chronic active type	13 (36.1)
	Chronic intermittent type	11 (30.6)
	Acute severe type	4 (11.1)
Clinical Activity score (Median)		6 (5-16)
Endoscopic Mayo score (Median)		2 (2-3)
CRP (mg/dl) (Median)		0.58 (0.02-13.44)
Medication at initiating SASP treatment (%)	Sustained release mesalazine	9 (25.0)
	Delayed release mesalazine	27 (75.0)
	Enema foam	14 (38.9)
	Corticosteroid	2 (5.6)
	Thiopurine	10 (27.8)
	GMAA	4 (11.1)
	Tacrolimus	4 (11.1)
	Anti TNF- $\alpha$ agent	6 (16.7)
History of Medication (%)	Corticosteroid	17 (47.2)
	Thiopurine	12 (33.3)
	GMAA	10 (27.8)
	Tacrolimus	8 (22.2)
	Anti TNF- $\alpha$ agent	10 (27.8)
Duration of Medication (months) (Median)*	Mesalazine	20.8 (0.5-247.2)
	Corticosteroid	11.7 (3.1-48.8)
	Thiopurine	11.2 (1.8-205.7)
	GMAA	2.1 (0.9-17.6)
	Tacrolimus	2.1 (0.3-17.2)
	Anti TNF- $\alpha$ agent	16.5 (0.3-61.0)

\*The median duration of medication in UC patients who had a history of treatment with mesalazine, corticosteroid, thiopurine, GMAA, tacrolimus and anti TNF- $\alpha$  agent, respectively.  
CRP, C-reactive protein; SASP, Salazosulfapyridine; GMAA, Granulocyte monocyte adsorption apheresis; TNF, tumor necrosis factor.

reactive protein (CRP) was 0.58 mg/dl at initiation of SASP treatment. Upon initiation of SASP treatment, 9 (25.0%) and 27 (75.0%) of the 36 UC patients were being treated with 4 g of sustained-release mesalazine and 3.6 g of delayed-release mesalazine, respectively, and 14 (38.9%) were being treated concomitantly with 1 g of mesalazine enema foam. Additional drugs included corticosteroids in 2 (5.6%), thiopurine in 10 (27.8%), GMAA in 4 (11.1%), tacrolimus in 4 (11.1%) and an anti-TNF- $\alpha$  agent in 6 (16.7%). The proportion of patients with a history of corticosteroid therapy was 47.2%. Furthermore, 33.3%, 27.8%, 22.2%, and 27.8% of the UC patients enrolled in this study had a history of treatment with thiopurine, GMAA, tacrolimus, or anti TNF- $\alpha$  agent, respectively. In UC patients who had been treated with mesalazine, corticosteroid, thiopurine, GMAA, tacrolimus, or anti TNF- $\alpha$  agent, the median treatment duration was 20.8 months, 11.7 months, 11.2 months, 2.1 months, 2.1 months, or 16.5 months, respectively.

### Differences in patient characteristics after initiating SASP treatment

The patient's characteristics between pre-SASP and post-SASP treatment are shown in [table 2](#). After initiating treatment with SASP, the median clinical activity score decreased from 6 (range 5–16) to 2 (range 0–16;  $p<0.001$ ). The median CRP level also decreased from 0.58 mg/dl (range: 0.02–13.44) to 0.16 mg/dl (range: 0.02–7.64;  $p=0.021$ ). Clinical remission was achieved in 25 (69.4%) of the 36 patients with UC, although adverse events occurred in 2 of these 25 patients. The median time to clinical remission was 1.1 months (range 0.4–7.3) after initiating SASP treatment. The remaining 11 patients with UC required therapy escalation, including GMAA, corticosteroid or an anti-TNF- $\alpha$  agent, because active UC was sustained after SASP treatment. In 9 (64.3%) of the 14 patients with UC treated with concomitant mesalazine enema prior to induction of SASP, the mesalazine enemas could be discontinued because the patients achieved clinical remission. In all four

**Table 2** Differences in the patient characteristics after initiating SASP treatment

Pre-SASP treatment		Post-SASP treatment	
Clinical Activity score (median)	6 (5-16)	Clinical Activity score (median)	2 (0-16)
CRP (median)	0.58 (0.02-13.44)	Clinical Remission (%)	25 (69.4)
Medications (%)		CRP (median)	0.16 (0.02-7.64)
Sustained release mesalazine	9 (25.0)	Medications (%)	
Delayed release mesalazine	27 (75.0)	Sustained release mesalazine	3 (9.4)
Enema foam	14 (38.9)	Delayed release mesalazine	8 (22.2)
SASP	0	Enema foam	5 (13.9)
Corticosteroid	2 (5.6)	SASP	29 (80.6)
Thiopurine	10 (27.8)	Corticosteroid	1 (2.8)
GMAA	4 (11.1)	Thiopurine	10 (27.8)
Tacrolimus	4 (11.1)	GMAA	2 (5.6)
Anti TNF- $\alpha$ agent	6 (16.7)	Tacrolimus	0 (0)
		Anti TNF- $\alpha$ agent	4 (11.1)

CRP, C-reactive protein; SASP, Sulfasalazine; GMAA, Granulocyte monocyte adsorption apheresis; TNF: tumor necrosis factor.

**Table 3** Clinical factors associated with the efficacy of SASP in refractory-UC patients

		CR n=25	Non-CR n=11	p-value
Gender (M/F)		19/6	8/3	1
Age (year) (Median)		42 (18-76)	31 (20-85)	0.95
Disease Duration (year) (Median)		2.0 (0.1-20.3)	0.3 (0-18.8)	0.174
Extent of Disease (%)				
	Extensive colitis	13 (52.0)	8 (72.7)	0.583
	Left-sided	11 (44.0)	2 (18.2)	
	Proctitis	1 (4.0)	1 (9.1)	
Clinical Course (%)				
	Initial attack type	3 (12.0)	5 (45.5)	0.395
	Chronic active type	10 (40.0)	3 (27.3)	
	Chronic intermittent type	9 (36.0)	2 (18.2)	
	Acute severe type	3 (12.0)	1 (9.1)	
Clinical Activity score (Median)		6 (5-11)	9 (5-16)	0.024
Endoscopic Mayo score (Median)		2 (2-3)	2 (2-3)	0.628
CRP (mg/dl) (Median)		0.42 (0.02-7.56)	0.89 (0.25-13.44)	0.012
SASP (%)				
	Change to SASP	15 (60.0)	10 (90.9)	0.116
	Addition of SASP	10 (40.0)	1 (9.1)	
Medication prior to initiating SASP (%)				
	Corticosteroid	1 (4.0)	1 (9.1)	0.524
	Thiopurine	10 (40.0)	0	0.016
	GMAA	2 (8.0)	2 (18.2)	0.57
	Tacrolimus	3 (12.0)	1 (9.1)	1
	Anti TNF- $\alpha$ agent	5 (20.0)	1 (9.1)	0.643
History of medication (%)				
	Corticosteroid	13 (52.0)	4 (36.4)	0.481
	Thiopurine	10 (40.0)	2 (18.2)	0.268
	GMAA	8 (32.0)	2 (18.2)	0.688
	Tacrolimus	6 (24.0%)	2 (18.2)	1
	Anti TNF- $\alpha$ agent	9 (36.0)	1 (9.1)	0.127

CR, clinical remission; CRP, C-reactive protein; SASP, sulphasalazine; GMAA, Granulocyte monocyte adsorption apheresis; TNF, tumor necrosis factor.

patients treated with tacrolimus prior to induction of SASP, the tacrolimus could be tapered off completely after beginning SASP treatment. In 20 of the 26 UC patients who could achieve clinical remission with SASP treatment, moreover, endoscopic examination was

performed before and after initiating treatment with SASP. In the 20 UC patients evaluated with endoscopic examination, 15 (75%) patients could achieve mucosal healing, such as Mayo-0, 1, after administering SASP (Supplemental Figure 1).

### Clinical factors associated with the efficacy of SASP in refractory-UC patients

To investigate the clinical factors associated with the efficacy of SASP in refractory-UC patients, we evaluated patient characteristics, such as sex, age, disease duration, extent of disease, clinical course of UC, clinical activity score, endoscopic Mayo score, CRP level, SASP treatment, medication prior to initiating SASP, and history of medication, between the clinical remission and non-clinical remission groups. The clinical activity score and the CRP level at the initiation of SASP treatment were significantly lower ( $p=0.024$  and  $p=0.012$ , respectively) and the number of patients treated with thiopurine was significantly higher ( $p=0.016$ ) in the clinical remission group than in the non-clinical remission group (table 3). Although all UC patients treated with thiopurine had a history of corticosteroid treatment (data not shown), the ratio of UC patients with a history of corticosteroid treatment was not significantly different between the clinical remission and non-clinical remission groups ( $p=0.481$ ). Regarding treatment with SASP, the ratio of patients who added low-dose SASP treatment to their mesalazine regimen tended to be higher in the clinical remission group than in the non-remission group, but the difference was not significant ( $p=0.116$ ). To evaluate the impact of clinical factors such as clinical activity of UC and thiopurine use on the efficacy of SASP, the difference in the clinical remission rate based on the clinical activity score was also evaluated between thiopurine use and non-use. Of 26 patients with UC with a low Lichtiger index score ( $\leq 7$ ), 21 (80.8%) achieved clinical remission (table 4). In the thiopurine non-use group, the clinical remission rate was significantly higher in those with a low disease activity score than in those with a high disease activity score ( $p=0.038$ ).

### Multivariate analysis for identifying predictive factors for efficacy of SASP

To evaluate whether the clinical activity score and thiopurine use could be predictive factors for the efficacy of SASP in refractory-UC patients, we performed a multivariate analysis using the Cox regression. Cox regression analysis suggested that a low clinical activity score ( $\leq 7$ ) and thiopurine use were predictive factors for the efficacy of SASP in refractory-UC patients, although there was no statistical significance (table 5; clinical activity score: HR 1.708; 95% CI 0.577 to 5.061,  $p=0.334$ ; thiopurine use: HR 1.151, 95% CI 0.506 to 2.618,  $p=0.737$ ). Therefore, these data suggest that SASP treatment is more useful for UC patients with a low clinical activity score and/or thiopurine use.

### Adverse events

In total, 7 (19.4%) of the 36 patients with refractory-UC experienced adverse events, including allergy ( $n=3$ ), hepatic dysfunction ( $n=2$ ) and exacerbation of UC ( $n=2$ ; table 6). The adverse events improved after reducing or discontinuing SASP. Moreover, the adverse event rate

**Table 4** The difference of clinical remission rate based on clinical activity score between thiopurine used and non-used group

Thiopurine	CAI score	CR (n=25)	non-CR (n=11)	p-value
Use	$\leq 7$ (%)	8	0	1
	$> 8$ (%)	2	0	
Non-use	$\leq 7$ (%)	13	5	0.038
	$> 8$ (%)	2	6	

CAI, clinical activity; CR, clinical remission.

**Table 5** Multivariate analysis for the efficacy of SASP

	Hazard Ratio	p-value	95% CI	
Clinical Activity $\leq 7$	1.708	0.334	0.577	5.061
Thiopurine use	1.151	0.737	0.506	2.618

CI, confidence interval.

**Table 6** Adverse events

	Total n=36	Thiopurine +(n=10)	Thiopurine -(n=26)	p-value
Allergy	3 (8.3)	1 (10.0)	2 (7.7)	1
Hepatic dysfunction	2 (5.6)	0 (0)	2 (7.7)	1
Exacerbation of UC	2 (5.6)	0 (0)	2 (7.7)	1
Total	7 (19.4)	1 (10.0)	6 (23.1)	0.645

UC, ulcerative colitis.

tended to be higher in patients without thiopurine treatment than in those with thiopurine treatment, although the difference was not statistically significant (thiopurine use: 10.0%, thiopurine non-use: 23.1%,  $p=0.645$ ).

### DISCUSSION

Our findings demonstrated that 69.4% of refractory-UC patients achieved clinical remission after initiating treatment with SASP. Moreover, low UC disease activity as indicated by a low clinical activity score and low CRP level, and thiopurine use might be predictive factors for the efficacy of SASP. Therefore, our data suggested that SASP is more effective and more suitable for UC patients with a low disease activity score and/or thiopurine use, and may allow these UC patients to avoid therapy escalation.

When considering treatment with SASP for patients with UC, gastroenterologists should pay attention to adverse events, including headache, nausea, skin rash, fever, hepatic dysfunction, aplastic anaemia, leucopenia, folate deficiency, pancreatitis, systemic lupus syndrome, Stevens-Johnson syndrome, pulmonary dysfunction and male infertility.<sup>23 24</sup> Adverse events occurred in 21.9% of



patients with UC treated with SASP. Therefore, SASP, an agent with positive and negative attributes, should be used for appropriate patients with intensive follow-up, and identifying those patients with UC most likely to benefit from SASP treatment is important. Our data, including a multivariate analysis, suggested that a low UC disease activity score and thiopurine use are predictive factors for the efficacy of SASP treatment in patients with UC. SASP has synergistic effects with immunosuppressive therapies including thiopurine agents.<sup>32,33</sup> Moreover, the adverse event rate of patients with UC with concomitant thiopurine therapy was lower than in those without it. Therefore, SASP treatment might be more suitable for patients with UC treated with immunosuppressive therapies, although intensive follow-up is required.

Several papers have reported that SASP at a dose of 2–4 g/day is effective for 40–80% of patients with mildly to moderately active UC.<sup>21,22,34,35</sup> SASP acts largely as a prodrug delivery system.<sup>19</sup> Almost 10% of SASP appears to be absorbed in the small bowel, and the remaining 90% reaches the colon.<sup>19</sup> This prodrug permits the release of 5-ASA in the colonic lumen with destruction of an azo-bound by azoreductases from luminal microflora.<sup>36</sup> The anti-inflammatory effect of 5-ASA is based on the mucosal concentration of 5-ASA in patients with UC, because the mucosal concentration of 5-ASA is inversely proportional to the disease activity of UC.<sup>27</sup> Moreover, SASP delivers a high concentration of 5-ASA to the colonic lumen compared with controlled-release mesalazine.<sup>25,26</sup> According to the present study, SASP was effective in 69.4% of patients with UC despite previous treatment with 3.6–4 g of oral mesalazine. Thus, SASP would be useful for patients with UC who are refractory to mesalazine because it delivers a high concentration of 5-ASA to the colonic lumen. On the other hand, it is unclear whether the therapeutic effect of SASP is based on the mucosal concentration of 5-ASA alone. In our study, the number of patients with UC who added SASP to their existing medication was higher in the clinical remission group than in the non-clinical remission group. This finding suggests that increasing the mucosal concentration of 5-ASA by adding SASP contributes to a more positive clinical outcome of patients with UC. SASP was also effective in patients with UC treated concomitantly with mesalazine enemas, which could deliver a high concentration of 5-ASA to the colonic mucosa. Tacrolimus could be tapered off completely after the induction of SASP treatment in patients with UC treated with tacrolimus prior to the induction of SASP, thereby avoiding therapy escalation with compounds such as anti-TNF- $\alpha$  agents. SASP, but not mesalazine, was recently reported to have novel therapeutic effects related to oxidative stress.<sup>37</sup> Furthermore, SASP exerts its effects mainly by the active antimicrobial component sulphapyridine,<sup>38</sup> which would alter the microbiota in UC patients, resulting in a better clinical outcome. These data suggests that SASP has additional anti-inflammatory effects that mesalazine does not have.

Our study has several limitations in terms of the methodology used; for example, this was a single-centre study, a very heterogeneous population of patients with different history of medications and different clinical course of disease was included, and it was a retrospective study. The number of UC-patients was too small to draw scientific conclusions. Furthermore, there was no control group in this retrospective study. The indication criteria of SASP for UC patients were also unclear. Moreover, we could not evaluate the concentration of 5-ASA in the colonic mucosa before or after initiating SASP treatment. Therefore, our data should be carefully interpreted, and further prospective studies with a larger number of patients are required for clarifying the efficacy of SASP for UC patients.

In conclusion, our data suggested the possibility of combination treatment with SASP and thiopurine as the alternative option for refractory-UC patients, particularly those with a low clinical activity score.

**Contributors** Enclosed is a manuscript by Yoshino *et al* entitled 'The usefulness of sulphasalazine for patients with ulcerative colitis refractory to mesalazine'. All authors have approved submission of this manuscript, and the material has not been previously reported. TY extracted and analysed the clinical data, and drafted the manuscript. MS also participated in extracting and analysing the clinical data. SY revised this manuscript critically for important intellectual content, and gave final approval of the version to be published.

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