

Efficacy and Safety of Azathioprine in Ulcerative Colitis with 5-aminosalicylic acid Intolerance: A Single-Center Retrospective Cohort Study

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Abstract

Background

5-aminosalicylic acid (5-ASA) intolerance can limit the use of standard maintenance therapy in patients with ulcerative colitis (UC). Although azathioprine is an established maintenance treatment, its efficacy and safety in patients with 5-ASA intolerance remain unclear.

Methods

We conducted a single-center retrospective cohort study of patients with UC who received azathioprine as maintenance therapy between April 2014 and December 2023. Patients were classified into 5-ASA-intolerant and 5-ASA-tolerant groups. The primary endpoint was azathioprine continuation after treatment initiation. Secondary endpoints included risk factors for azathioprine discontinuation, azathioprine-associated adverse events, azathioprine continuation excluding adverse event-related discontinuation, and endoscopic outcomes.

Results

Sixty-six patients were included: 15 were 5-ASA-intolerant and 51 were 5-ASA-tolerant. During median follow-up periods of 805 and 431 days, respectively, azathioprine was discontinued in 41 patients: 25 because of relapse and 16 because of adverse events. The cumulative azathioprine continuation rates at 1 and 3 years were 60.0% and 52.5%, respectively, in the 5-ASA-intolerant group and 52.6% and 46.3%, respectively, in the 5-ASA-tolerant group, with no significant difference between groups (log-rank $p = 0.404$). 5-ASA intolerance was not associated with azathioprine discontinuation (hazard ratio, 0.71; 95% confidence interval, 0.31–1.61; $p = 0.407$) or azathioprine-associated adverse events (odds ratio, 1.82; 95% confidence interval, 0.51–6.44; $p = 0.354$). After excluding adverse event-related discontinuations, the 1- and 3-year continuation rates were 90.0% and 78.8%, respectively, in the 5-ASA-intolerant group and 67.2% and 59.1%, respectively, in the 5-ASA-tolerant group (log-rank $p = 0.094$). At least 1 year after azathioprine initiation, Mayo Endoscopic Subscore (MES) 0–1 was achieved by 7 of 15 patients in the 5-ASA-intolerant group and 16 of 51 patients in the 5-ASA-tolerant group, while MES 0 was achieved by 4 and 12 patients, respectively; 5-ASA intolerance was not associated with either MES 0–1 ($p = 0.279$) or MES 0 ($p = 0.803$).

Conclusions

Azathioprine demonstrated comparable long-term treatment continuation, safety, and endoscopic outcomes in patients with and without 5-ASA intolerance. These findings suggest that azathioprine may be an effective maintenance treatment option for patients with UC who are intolerant to 5-ASA.

Introduction

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease of unknown etiology [1]. Following remission induction, long-term management aimed at preventing relapse and maintaining clinical remission and endoscopic healing is essential [2]. Oral 5-aminosalicylic acid (5-ASA) is the first-line therapy for both the induction and maintenance of remission in patients with mild-to-moderate UC [3]. 5-ASA exerts its therapeutic effects locally within the colonic mucosa through anti-inflammatory and immunomodulatory mechanisms [4]. Owing to its favorable efficacy and safety profile, it remains a cornerstone of UC treatment [5].

Despite its widespread use, some patients develop intolerance to oral 5-ASA formulations. The reported incidence of 5-ASA intolerance is less than 20% among patients with UC [6, 7]. Common manifestations include worsening diarrhea, fever, abdominal pain, and bloody stools, which typically occur within days of treatment initiation [8, 9]. In some cases, severe adverse events such as interstitial nephritis and pancreatitis may occur [6]. Furthermore, 5-ASA intolerance has been associated with poorer UC outcomes, increased use of immunosuppressive therapies, dysbiosis, and a higher risk of colectomy [10–14].

Azathioprine is an established immunomodulator for the maintenance of remission in UC [15]. Although the use of biologics and small-molecule therapies has expanded considerably, azathioprine remains an important treatment option because of its proven efficacy, widespread availability, and extensive long-term clinical experience [16]. Patients with 5-ASA intolerance may require earlier initiation of azathioprine because continued treatment with 5-ASA is often not feasible [14]. However, evidence regarding the efficacy and safety of azathioprine specifically in patients with 5-ASA intolerance remains limited.

To the best of our knowledge, no study has directly compared azathioprine outcomes between patients with and without 5-ASA intolerance. Therefore, we conducted a retrospective cohort study to evaluate the efficacy and safety of azathioprine in patients with UC and 5-ASA intolerance. Specifically, we compared azathioprine continuation rates between patients with and without 5-ASA intolerance and investigated factors associated with azathioprine discontinuation, azathioprine-associated adverse events, and endoscopic outcomes.

Methods

Patients

The aim of this study was to compare the effectiveness and safety of azathioprine between patients with UC with and without 5-ASA intolerance. This retrospective cohort study included patients with UC who received azathioprine treatment at a single tertiary referral center in Japan, between April 1, 2014, and December 31, 2023. All patients were aged ≥ 20 years and had been diagnosed with UC based on standard clinical, endoscopic, and histopathological findings according to the diagnostic criteria established by the Research Committee of Inflammatory Bowel Disease in Japan [17].

Patients were excluded if the extent of disease was unknown, the date of azathioprine initiation was unavailable, concomitant medications at azathioprine initiation were unknown, advanced therapies other than tacrolimus were administered concomitantly with azathioprine at treatment initiation, or follow-up was < 6 months in the absence of documented azathioprine discontinuation.

Medical records were retrospectively reviewed by two gastroenterologists. Any discrepancies in data collection or outcome assessment were resolved through discussion between the two reviewers until consensus was reached.

Data collection and definitions

Eligible patients were identified using both the electronic medical record system and the institutional ulcerative colitis database to ensure complete case ascertainment. Demographic and clinical data were extracted from medical records, including sex, age at diagnosis, Patient-Reported Outcome 2 (PRO2) score [18], disease extent, 5-ASA intolerance, history of acute severe ulcerative colitis (ASUC) [19], concomitant medications at azathioprine initiation, time from diagnosis to azathioprine initiation, azathioprine dose, previous biologic exposure, Mayo Endoscopic Subscore (MES) after azathioprine initiation, and reasons for azathioprine discontinuation, including relapse and adverse events.

The PRO2 score was calculated as the sum of the rectal bleeding and stool frequency subscore of the Mayo score [18]. A history of ASUC was defined according to the Modified Truelove and Witts criteria [19].

An azathioprine-associated adverse event was defined as any symptom or laboratory abnormality considered by the treating physician to be attributable to azathioprine that developed after treatment initiation and resolved following drug discontinuation.

5-ASA intolerance was defined as meeting either of the following criteria: (1) the occurrence of an adverse event within 6 months of initiation of the first oral 5-ASA preparation, resulting in the inability to continue oral 5-ASA because of intolerance upon rechallenge; or (2) the absence of rechallenge because the initial adverse event was severe or associated with substantial organ toxicity. In contrast, 5-ASA tolerance was defined as either the absence of adverse events attributable to 5-ASA or the ability to continue oral 5-ASA for at least 6 months after rechallenge despite a previous adverse event. Eligible patients were classified as either the 5-ASA-intolerant group or the 5-ASA-tolerant group. Relapse was defined as the initiation of prednisolone at a dose equivalent to ≥ 20 mg/day for remission induction after azathioprine initiation or the initiation of an advanced therapy for active UC. Azathioprine discontinuation was defined as discontinuation due to either adverse events or relapse. Advanced therapies included anti-tumor necrosis factor- α agents, anti-interleukin-12/23 antibodies, anti-interleukin-23 antibodies, Janus kinase inhibitors, sphingosine-1-phosphate receptor modulators, anti- $\alpha 4\beta 7$ integrin antibodies, and calcineurin inhibitors.

Study design and statistical analyses

This single-center retrospective observational study included patients who received azathioprine for the maintenance therapy of UC.

The primary endpoint was azathioprine continuation after treatment initiation in the 5-ASA-intolerant and 5-ASA-tolerant groups. The secondary endpoints were (1) identification of risk factors for azathioprine discontinuation, (2) identification of risk factors for azathioprine-associated adverse events, (3) comparison of azathioprine continuation between the 5-ASA-intolerant and 5-ASA-tolerant groups after excluding patients who discontinued azathioprine because of adverse events, and (4) identification of factors associated with achieving a MES of 0 and MES of 0–1 at least 1 year after azathioprine initiation.

Baseline characteristics and study outcomes were compared between the 5-ASA-intolerant and 5-ASA-tolerant groups. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using the Mann–Whitney U test.

Azathioprine continuation was analyzed using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test. Risk factors for azathioprine discontinuation were evaluated using Cox proportional hazards regression analysis. Risk factors for azathioprine-associated adverse events, as well as factors associated with achieving MES 0 and MES 0–1, were evaluated using logistic regression analysis. Multivariable analyses were not performed because of the limited number of patients with 5-ASA intolerance and the resulting risk of model overfitting.

No formal sample size calculation was performed because this was a retrospective study including all eligible patients during the study period. All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics, version 31.0.0.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 119 patients with UC who received azathioprine for maintenance therapy were initially identified. Of these, 42 patients were excluded because of insufficient clinical data, 10 because of concomitant use of advanced therapies with azathioprine, and 1 because azathioprine had been prescribed for an indication other than UC. Consequently, 66 eligible patients were included in the analysis, comprising 15 patients in the 5-ASA-intolerant group and 51 patients in the 5-ASA-tolerant group (Fig. 1).

Baseline patient characteristics are summarized in Table 1. The median age at diagnosis was 31 years (Interquartile range [IQR], 23–49 years) in the 5-ASA-intolerant group and 38 years (IQR, 28–51 years) in

the 5-ASA-tolerant group ($p = 0.413$). The median PRO2 score was 0 (IQR, 0–1) and 0 (IQR, 0–3), respectively ($p = 0.171$).

Table 1
Baseline Patient Characteristics

	Overall	5-ASA-intolerant group	5-ASA-tolerant group	Univariate analysis		
	(n = 66)	(n = 15)	(n = 51)	Odds Ratio	95%CI	p value
Male sex, n (%)	34	7 (46.7)	27 (52.9)	0.778	0.245–2.466	0.772
Age at diagnosis, years; median (IQR)	33.5 (23.8–49.0)	31(23–49)	38(28–51)			0.413
PRO2 score; median (IQR)	0 (0–2)	0 (0–1)	0 (0–3)			0.171
Disease extent						
Extensive colitis, n (%)	47	8 (53.3)	39 (76.5)	0.352	0.106–1.171	0.108
Left-sided colitis, n (%)	15	4 (26.7)	11 (21.6)	1.322	0.352–4.973	0.731
Proctitis, n (%)	1	1 (6.7)	0 (0)	1.071	0.936–1.227	0.227
Right-sided or segmental colitis, n (%)	3	2 (13.3)	1 (2.0)	7.692	0.646–91.562	0.127
History of ASUC, n (%)	28	7 (46.7)	21 (41.2)	1.25	0.393–3.978	0.771
Concomitant medications at azathioprine initiation						
Corticosteroids, n (%)	49	9(60)	40(78.4)	0.413	0.121–1.411	0.185
Tacrolimus, n (%)	6	0(0)	6(11.8)	0.882	0.798–0.975	0.323
Leukocytapheresis, n (%)	2	0(0)	2(3.9)	0.961	0.909–1.016	1
Time to azathioprine initiation, days; median(IQR)	1201 (191–3811)	69 (40–258)	1513 (608–5120)			< 0.001
Azathioprine dose, mg/day; median (IQR)	50 (50–50)	50 (50–50)	50 (50–100)			0.017
Previous biologic exposure						

	Overall	5-ASA-intolerant group	5-ASA-tolerant group	Univariate analysis		
	(n = 66)	(n = 15)	(n = 51)	Odds Ratio	95%CI	p value
Infliximab, n (%)	3	0 (0)	3 (5.9)	0.941	0.879–1.008	1
5-ASA, 5-aminosalicylic acid; PRO2, Patient-Reported Outcome 2; ASUC, Acute Severe Ulcerative Colitis; IQR, interquartile range; CI, confidence interval.						

Patients in the 5-ASA-intolerant group were less likely to have extensive colitis than those in the 5-ASA-tolerant group (53.3% vs. 76.5%), although the difference did not reach statistical significance ($p = 0.108$). No significant differences were observed between the groups with respect to sex, disease extent, history of acute severe UC, concomitant medications at azathioprine initiation, or previous infliximab exposure.

The median time from UC diagnosis to azathioprine initiation was significantly shorter in the 5-ASA-intolerant group than in the 5-ASA-tolerant group (69 days [IQR, 40–258] vs. 1,513 days [IQR, 608–5,120; $p < 0.001$]). In addition, the azathioprine dose at initiation was significantly lower in the 5-ASA-intolerant group than in the 5-ASA-tolerant group (50 mg/day [IQR, 50–50] vs. 50 mg/day [IQR, 50–100]; $p = 0.017$).

Azathioprine Continuation

The median follow-up period was 805 days (IQR, 68–1,967 days) in the 5-ASA-intolerant group and 431 days (IQR, 80–1,633 days) in the 5-ASA-tolerant group. During follow-up, azathioprine was discontinued in 41 of 66 patients. The most common reason for discontinuation was relapse (25/41, 61.0%), followed by adverse events (16/41, 39.0%). The most frequent adverse events leading to discontinuation were liver dysfunction ($n = 4$), nausea ($n = 3$), and myelosuppression ($n = 3$). Other adverse events included fatigue ($n = 2$), cellulitis ($n = 1$), hypertension ($n = 1$), pancreatitis ($n = 1$), and enteritis ($n = 1$).

Kaplan–Meier analysis of azathioprine continuation is shown in Fig. 2. The cumulative azathioprine continuation rates at 1 and 3 years were 60.0% and 52.5%, respectively, in the 5-ASA-intolerant group, compared with 52.6% and 46.3%, respectively, in the 5-ASA-tolerant group. No significant difference in azathioprine continuation was observed between the two groups (log-rank test, $p = 0.404$).

Risk Factors for Azathioprine Discontinuation

The results of the univariate Cox proportional hazards regression analysis for risk factors associated with azathioprine discontinuation are shown in Table 2. No baseline characteristic was significantly associated with azathioprine discontinuation. Specifically, 5-ASA intolerance was not associated with an increased risk of azathioprine discontinuation (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.31–1.61; $p = 0.407$). Likewise, age at diagnosis, PRO2 score, disease extent, history of acute severe UC,

concomitant medications at azathioprine initiation, time from diagnosis to azathioprine initiation, and azathioprine dose were not significantly associated with discontinuation.

Table 2
Risk Factors for Azathioprine Discontinuation

	Univariate analysis		
	Hazard Ratio	95% confidence interval	p value
Male sex, n (%)	0.821	0.440–1.531	0.534
Age at diagnosis, years; median (IQR)	1.003	0.983–1.024	0.74
PRO2 score; median (IQR)	0.997	0.826–1.204	0.977
Disease extent			
Extensive colitis, n (%)	1.350	0.673–2.709	0.398
Left-sided colitis, n (%)	0.749	0.355–1.579	0.448
Proctitis, n (%)	0.048	0.00-1164.3	0.556
Right-sided or segmental colitis, n (%)	1.252	0.301–5.205	0.758
5-ASA intolerance, n (%)	0.707	0.311–1.606	0.407
History of ASUC, n (%)	1.343	0.716–2.518	0.358
Concomitant medications at azathioprine initiation			
Corticosteroids, n (%)	0.784	0.390–1577	0.495
Tacrolimus, n (%)	1.990	0.776–5.102	0.152
Leukocytapheresis, n (%)	0.608	0.083–4.435	0.623
Time to azathioprine initiation, days; median(IQR)	1.000	1.000–1.000	0.328
Azathioprine dose, mg/day; median (IQR)	0.993	0.976–1.010	0.42
Previous biologic exposure			
Infliximab, n (%)	2.938	0.895–9.647	0.076
5-ASA, 5-aminosalicylic acid; PRO2, Patient-Reported Outcome 2; ASUC, Acute Severe Ulcerative Colitis; IQR, interquartile range.			

Previous infliximab exposure showed a trend toward an increased risk of azathioprine discontinuation (HR, 2.94; 95% CI, 0.90–9.65; p = 0.076), although the association did not reach statistical significance.

Risk Factors for Azathioprine-Associated Adverse Events

The results of the univariate logistic regression analysis for risk factors associated with azathioprine-associated adverse events are shown in Table 3. Among the variables examined, a lower azathioprine dose was significantly associated with the occurrence of adverse events (odds ratio [OR], 0.943; 95% CI, 0.895–0.993; $p = 0.025$).

Table 3
Risk Factors for Azathioprine-Associated Adverse Events

	With adverse events	Without adverse events	Univariate analysis		
	(n = 16)	(n = 50)	Odds Ratio	95%CI	p value
Male sex, n (%)	6	28	0.471	0.148– 1.498	0.202
Age at diagnosis, years; median (IQR)	44 (22.75– 51.75)	32.5 (23.75– 48)	1.017	0.979– 1.056	0.383
PRO2 score; median (IQR)	0 (0–1)	0 (0–2)	0.768	0.509– 1.158	0.208
Disease extent					
Extensive colitis, n (%)	12	35	1.286	0.356– 4.639	0.701
Left-sided colitis, n (%)	3	12	0.731	0.178– 3.003	0.664
Proctitis, n (%)	0	1	Not estimable		1.000
Right-sided or segmental colitis, n (%)	1	2	1.600	0.135– 18.906	0.709
5-ASA intolerance, n (%)	5	10	1.818	0.514– 6.436	0.354
History of ASUC, n (%)	7	21	1.074	0.345– 3.346	0.902
Concomitant medications at azathioprine initiation					
Corticosteroids, n (%)	10	39	0.470	0.140– 1.582	0.223
Tacrolimus, n (%)	2	4	1.643	0.272– 9.936	0.589
Leukocytapheresis, n (%)	0	2	Not estimable		0.999
Time to azathioprine initiation, days; median(IQR)	905.5 (280–3466)	1293.5 (118.75– 4875.25)	1.000	1.000– 1.000	0.799
Azathioprine dose, mg/days; median (IQR)	50 (31.25– 50)	50 (50–75)	0.943	0.895– 993	0.025

	With adverse events	Without adverse events	Univariate analysis		
	(n = 16)	(n = 50)	Odds Ratio	95%CI	<i>p</i> value
Previous biologic exposure					
Infliximab, n (%)	2	1	7.000	0.590- 82.993	0.123
5-ASA, 5-aminosalicylic acid; PRO2, Patient-Reported Outcome 2; ASUC, Acute Severe Ulcerative Colitis; IQR, interquartile range; CI, confidence interval. Odds ratios were calculated for the presence versus absence of each factor.					

5-ASA intolerance was not significantly associated with azathioprine-associated adverse events (OR, 1.82; 95% CI, 0.51–6.44; $p = 0.354$). Likewise, sex, age at diagnosis, PRO2 score, disease extent, history of acute severe UC, concomitant medications at azathioprine initiation, time from diagnosis to azathioprine initiation, and previous infliximab exposure were not significantly associated with the occurrence of adverse events.

Azathioprine Continuation Excluding Discontinuation Due to Adverse Events

After excluding patients who discontinued azathioprine because of adverse events, the median follow-up period was 1,599.5 days (IQR, 745.5–1,996.8 days) in the 5-ASA-intolerant group and 933.5 days (IQR, 217.5–3,177.0 days) in the 5-ASA-tolerant group. During follow-up, azathioprine was discontinued in 25 patients.

Kaplan–Meier analysis of azathioprine continuation after excluding discontinuation due to adverse events is shown in Fig. 3. The cumulative azathioprine continuation rates at 1 and 3 years were 90.0% and 78.8%, respectively, in the 5-ASA-intolerant group, compared with 67.2% and 59.1%, respectively, in the 5-ASA-tolerant group. No significant difference in azathioprine continuation was observed between the two groups (log-rank test, $p = 0.094$).

Factors Associated with Endoscopic Improvement and Remission

Among the 66 eligible patients, 26 underwent a total of 105 colonoscopies at least 1 year after azathioprine initiation. Patients who did not undergo colonoscopy at least 1 year after azathioprine initiation were classified as non-achievers for the endoscopic outcomes. Overall, 23 patients achieved MES 0–1, and 16 achieved MES 0.

The results of the univariate logistic regression analyses for factors associated with achieving MES 0–1 and MES 0 at least 1 year after azathioprine initiation are shown in Tables 4 and 5, respectively.

Table 4
Factors Associated with Achievement of MES 0–1

	MES 0–1 achievers	MES 0–1 non- achievers	Univariate analysis		
	(n = 23)	(n = 43)	Odds Ratio	95%CI	p value
Male sex, n (%)	13 (56.5)	21 (48.8)	1.362	0.492– 3.771	0.552
Age at diagnosis, years; median (IQR)	41 (26–49)	31 (21–49)	1.018	0.984– 1.054	0.300
PRO2 score; median (IQR)			1.186	0.877– 1.604	0.269
Disease extent					
Extensive colitis, n (%)	15 (65.2)	32 (74.4)	0.645	0.215– 1.932	0.433
Left-sided colitis, n (%)	7 (30.4)	8 (18.6)	1.914	0.592– 6.193	0.279
Proctitis, n (%)	0 (0)	1 (2.3)	Not estimable		1.000
Right-sided or segmental colitis, n (%)	1 (4.3)	2 (4.7)	0.932	0.80- 10.860	0.955
5-ASA intolerance, n (%)	7 (30.4)	8 (18.6)	1.914	0.592– 6.193	0.279
History of ASUC, n (%)	8 (34.8)	20 (46.5)	0.613	0.215– 1.747	0.360
Concomitant medications at azathioprine initiation					
Corticosteroids, n (%)	19 (82.6)	30 (69.8)	2.058	0.584– 7.252	0.261
Tacrolimus, n (%)	1 (4.3)	5 (11.6)	0.345	0.038– 3.150	0.346
Leukocytapheresis, n (%)	1 (4.3)	1 (2.3)	1.909	0.114– 32.009	0.653
Time to azathioprine initiation, days; median(IQR)	1513 (77- 5120)	1007 (247– 3421)	1.000	1.000– 1.000	0.255
Azathioprine dose, mg/day; median (IQR)	50 (50–75)	50 (50–50)	1.020	0.994– 1.047	0.134
Previous biologic exposure					

	MES 0–1 achievers	MES 0–1 non- achievers	Univariate analysis		
	(n = 23)	(n = 43)	Odds Ratio	95%CI	<i>p</i> value
Infliximab, n (%)	3 (13.0)	0 (0)	Not estimable		0.999
5-ASA, 5-aminosalicylic acid; PRO2, Patient-Reported Outcome 2; MES, Mayo Endoscopic Subscore; ASUC, Acute Severe Ulcerative Colitis; IQR, interquartile range; CI, confidence interval. Odds ratios were calculated for the presence versus absence of each factor.					

Table 5
Factors Associated with Achievement of MES 0

	MES 0 achievers	MES 0 non- achievers	Univariate analysis		
	(n = 16)	(n = 50)	Odds Ratio	95%CI	p value
Male sex, n (%)	10 (62.5)	24 (48.0)	1.806	0.569– 5.726	0.316
Age at diagnosis, years; median (IQR)	40 (26.5– 54.0)	32.5 (22.75– 49.0)	1.022	0.984– 1.062	0.264
PRO2 score; median (IQR)	1 (0–2.75)	0 (0–2.00)	1.142	0.824– 1.584	0.425
Disease extent					
Extensive colitis, n (%)	9 (56.3)	38 (76.0)	0.406	0.125– 1.324	0.135
Left-sided colitis, n (%)	6 (37.5)	9 (18.0)	2.733	0.789– 9.473	0.113
Proctitis, n (%)	0 (0)	1 (2.0)	Not estimable		1.000
Right-sided or segmental colitis, n (%)	1 (6.3)	2 (4.0)	1.600	0.135– 18.906	0.709
Mesalamine intolerance, n (%)	4 (25.0)	11 (22.0)	1.182	0.317– 4.400	0.803
History of ASUC, n (%)	5 (31.3)	23 (46.0)	0.534	0.162– 1.762	0.303
Concomitant medications at azathioprine initiation					
Corticosteroids, n (%)	12 (75.0)	37 (74.0)	1.054	0.288– 3.852	0.937
Tacrolimus, n (%)	1 (6.3)	5 (10.0)	0.600	0.065– 5.553	0.653
Leukocytapheresis, n (%)	1 (6.3)	1 (2.0)	3.267	0.192– 55.438	0.413
Time to azathioprine initiation, days; median(IQR)	2036.5 (239.75– 6107)	1003.5 (191.25– 3436)	1.000	1.000– 1.000	0.140
Azathioprine dose, mg/day; median (IQR)	50 (50–50)	50 (50–50)	1.007	0.979– 1.035	0.643
Previous biologic exposure					

	MES 0 achievers	MES 0 non- achievers	Univariate analysis		
	(n = 16)	(n = 50)	Odds Ratio	95%CI	p value
Infliximab, n (%)	0 (0)	3 (6.0)	Not estimable		0.999
5-ASA, 5-aminosalicylic acid; PRO2, Patient-Reported Outcome 2; MES, Mayo Endoscopic Subscore; ASUC, Acute Severe Ulcerative Colitis; IQR, interquartile range; CI, confidence interval. Odds ratios were calculated for the presence versus absence of each factor.					

5-ASA intolerance was not associated with achieving MES 0–1 (OR, 1.914; 95% CI, 0.592–6.193; $p = 0.279$) or MES 0 (OR, 1.182; 95% CI, 0.317–4.400; $p = 0.803$). Likewise, sex, age at diagnosis, PRO2 score, disease extent, history of acute severe UC, concomitant medications at azathioprine initiation, time from diagnosis to azathioprine initiation, azathioprine dose, and previous infliximab exposure were not significantly associated with achieving MES 0–1 or MES 0.

Discussion

The present study evaluated the efficacy and safety of azathioprine in patients with UC according to 5-ASA intolerance status. We found that azathioprine continuation rates were comparable between the 5-ASA-intolerant and 5-ASA-tolerant groups. Furthermore, 5-ASA intolerance was not associated with azathioprine discontinuation, azathioprine-associated adverse events, or endoscopic outcomes. No significant baseline predictors of the study outcomes were identified.

The present study demonstrated that azathioprine continuation rates did not differ significantly between patients with and without 5-ASA intolerance. The cumulative azathioprine continuation rates in the 5-ASA-intolerant group were 60.0% and 52.5% at 1 and 3 years, respectively. These findings are consistent with previous evidence supporting the efficacy of thiopurines for the maintenance of remission in UC. A recent Cochrane review reported that azathioprine was superior to placebo for maintaining remission, with 56% of patients remaining in remission compared with 38% in the placebo group [15]. Furthermore, current clinical guidelines continue to recommend thiopurines as a maintenance treatment option for selected patients with UC [20]. Patients with 5-ASA intolerance often require alternative maintenance strategies because continued 5-ASA therapy is frequently not feasible. In the present study, 5-ASA intolerance was not associated with azathioprine discontinuation, suggesting that the long-term efficacy of azathioprine is not substantially affected by intolerance to 5-ASA. Collectively, these findings support the use of azathioprine as a maintenance treatment option for patients with UC and 5-ASA intolerance.

In the present study, 5-ASA intolerance was not associated with an increased risk of azathioprine-associated adverse events. Adverse events leading to azathioprine discontinuation occurred in 16 patients, with liver dysfunction, nausea, and myelosuppression being the most common causes. These findings are consistent with previous studies demonstrating that adverse events remain a major

limitation of thiopurine therapy in clinical practice and account for a substantial proportion of treatment discontinuations [21]. The lack of an association between 5-ASA intolerance and azathioprine-associated adverse events suggests that intolerance to 5-ASA does not necessarily predispose patients to intolerance of azathioprine. This observation may be explained by the distinct mechanisms underlying adverse reactions to these agents. Whereas 5-ASA intolerance is considered to involve drug-specific hypersensitivity reactions and may be influenced by pharmacogenetic susceptibility, including variants such as rs144384547 and loci near RGS17 [8, 22, 23], azathioprine-related adverse events are largely attributable to thiopurine metabolism and pharmacogenetic factors, particularly NUDT15 variants [24, 25]. Therefore, a history of 5-ASA intolerance alone should not preclude the use of azathioprine in patients who require maintenance therapy. Interestingly, a lower azathioprine dose was associated with adverse events in the present study. However, this finding should be interpreted with caution because patients who developed adverse events may have undergone dose reduction or treatment discontinuation before dose escalation, resulting in a lower recorded dose. Therefore, reverse causation cannot be excluded. Further studies are needed to clarify the relationship between azathioprine dose and treatment-related toxicity.

Endoscopic healing has emerged as an important therapeutic target in UC and is associated with improved long-term outcomes [2]. Among the entire study cohort, 23 patients achieved MES 0–1, and 16 achieved MES 0. However, no baseline factor, including 5-ASA intolerance, was significantly associated with achieving endoscopic improvement or remission. These findings should be interpreted with caution. Patients who did not undergo colonoscopy at least 1 year after azathioprine initiation were classified as non-achievers of MES 0–1 and MES 0. Because 30 of the 41 treatment failures occurred within the first year of therapy, these patients were automatically categorized as non-achievers. In contrast, among the 25 patients who remained on azathioprine for at least 1 year, 23 (92%) underwent endoscopic evaluation. Therefore, our analysis may have provided a conservative estimate of endoscopic remission rates by using the entire study cohort, rather than only patients who underwent follow-up colonoscopy, as the denominator. Previous studies have demonstrated the ability of thiopurines to achieve endoscopic healing in UC. In a multicenter cohort study of patients receiving thiopurine monotherapy, Prieux-Klotz et al. reported mucosal healing in 43.7% of patients and identified thiopurine exposure for at least 2 years as an independent predictor of mucosal healing [26]. In contrast, we did not identify any significant predictors of MES 0–1 or MES 0 achievement. This discrepancy may be explained by differences in study design, outcome definitions, and the limited sample size of the present study. Importantly, 5-ASA intolerance was not associated with poorer endoscopic outcomes. Further studies with larger sample sizes and standardized endoscopic follow-up protocols are warranted to clarify predictors of endoscopic remission during azathioprine therapy.

This study has some limitations. First, the retrospective single-center design may have introduced selection bias and limited the generalizability of the findings. Second, the relatively small number of patients with 5-ASA intolerance limited statistical power and precluded multivariable analyses. Third, thiopurine metabolite levels and NUDT15 genotypes were unavailable and therefore could not be

incorporated into the analysis. Finally, endoscopic follow-up was not performed according to a predefined protocol, which may have influenced the assessment of endoscopic outcomes.

Conclusion

In conclusion, the efficacy and safety of azathioprine were not substantially influenced by 5-ASA intolerance status in patients with UC. Azathioprine continuation rates, adverse-event profiles, and endoscopic outcomes were comparable between patients with and without 5-ASA intolerance. These findings support the use of azathioprine as a maintenance treatment option for patients with UC and 5-ASA intolerance. However, larger multicenter studies are warranted to confirm our results.

Abbreviations

UC: ulcerative colitis

5-ASA: 5-aminosalicylic acid

PRO2: Patient-Reported Outcome 2

MES: Mayo Endoscopic Subscore

ASUC: acute severe ulcerative colitis

IQR: interquartile range

HR: hazard ratio

CI: confidence interval

OR: odds ratio

Declarations

Ethics approval and consent to participate

The Ethics Committee of Tokyo Medical University approved this study (approval number: T2026-0014) on April 28, 2026. The study was conducted in accordance with the principles of the Declaration of Helsinki. Although the investigators had access to identifiable participant information during data collection, all data were anonymized prior to analysis. The requirement for written informed consent to participate was waived by the Ethics Committee of Tokyo Medical University because of the retrospective nature of the study and the use of an opt-out approach. Information regarding the study, including details of the opt-out process, was publicly disclosed on the website of Tokyo Medical University Hospital. No patients declined the use of their anonymized data for research purposes.

Consent for publication

Not applicable.

Availability of data and materials

The individual-level datasets generated and/or analyzed during the current study are not publicly available because they contain potentially identifiable clinical information, and consent for external data sharing was not obtained from the study participants. All relevant aggregated data supporting the findings of this study are included in this article.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AM conceptualized and designed the study, developed the methodology, performed the formal analysis, collected and curated the data, and drafted the manuscript. MF collected and curated the data, validated the data, and critically revised the manuscript. KU, TIch, SN, SK, YY, TMo, YK, and TMu collected and curated the data and critically revised the manuscript. TIt conceptualized the study, supervised the project, and critically revised the manuscript. All authors read and approved the final manuscript.

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References

1. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology*. 2004;126:451–9.
2. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology*. 2021;160:1570–83.
3. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis*. 2017;11:769–84.

4. Desreumaux P, Ghosh S. Review article: mode of action and delivery of 5-aminosalicylic acid – new evidence. *Aliment Pharmacol Ther.* 2006;24:2–9.
5. Ford AC, Achkar J-P, Khan KJ, et al. Efficacy of 5-aminosalicylates in ulcerative colitis: systematic review and meta-analysis. *Am J Gastroenterol.* 2011;106:601–16.
6. Ransford RAJ, Langman MJS. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut.* 2002;51:536–9.
7. Di Paolo MC, Paoluzi OA, Pica R, et al. Sulphasalazine and 5-aminosalicylic acid in long-term treatment of ulcerative colitis: report on tolerance and side-effects. *Dig Liver Dis.* 2001;33:563–9.
8. Mikami Y, Tsunoda J, Suzuki S, et al. Significance of 5-Aminosalicylic Acid Intolerance in the Clinical Management of Ulcerative Colitis. *Digestion.* 2023;104:58–65.
9. Matsumoto S, Mashima H. Mesalazine allergy and an attempt at desensitization therapy in patients with inflammatory bowel disease. *Sci Rep.* 2020;10:22176.
10. Chakraborty TK, Bhatia D, Heading RC, et al. Salicylate induced exacerbation of ulcerative colitis. *Gut.* 1987;28:613–5.
11. Sturgeon JB, Bhatia P, Hermens D, et al. Exacerbation of chronic ulcerative colitis with mesalamine. *Gastroenterology.* 1995;108:1889–93.
12. Kapur KC, Williams GT, Allison MC. Mesalazine induced exacerbation of ulcerative colitis. *Gut.* 1995;37:838–9.
13. Mizuno S, Ono K, Mikami Y, et al. 5-Aminosalicylic acid intolerance is associated with a risk of adverse clinical outcomes and dysbiosis in patients with ulcerative colitis. *Intest Res.* 2020;18:69–78.
14. Hibiya S, Matsuyama Y, Fujii T, et al. 5-aminosalicylate-intolerant patients are at increased risk of colectomy for ulcerative colitis. *Aliment Pharmacol Ther.* 2021;53:103–13.
15. Hasskamp J, Meinhardt C, Patton PH, et al. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2025;2:CD000478.
16. Pillai N, Dusheiko M, Burnand B, et al. A systematic review of cost-effectiveness studies comparing conventional, biological and surgical interventions for inflammatory bowel disease. *PLoS ONE.* 2017;12:e0185500.
17. Matsuoka K, Kobayashi T, Ueno F, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease. *J Gastroenterol.* 2018;53:305–53.
18. Jairath V, Khanna R, Zou GY, et al. Development of interim patient-reported outcome measures for the assessment of ulcerative colitis disease activity in clinical trials. *Aliment Pharmacol Ther.* 2015;42:1200–10.
19. Rivière P, Li Wai Suen C, Chaparro M, et al. Acute severe ulcerative colitis management: unanswered questions and latest insights. *Lancet Gastroenterol Hepatol.* 2024;9:251–62.

20. Singh S, Loftus EV Jr, Limketkai BN, et al. AGA Living Clinical Practice Guideline on Pharmacological Management of Moderate-to-Severe Ulcerative Colitis. *Gastroenterology*. 2024;167:1307–43.

21. Jharap B, Seinen ML, de Boer NK, et al. Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-year intercept cohorts. *Inflamm Bowel Dis*. 2010;16:1541–9.

22. Madarama A, Fukuzawa M, Uchida K, et al. Significance of the drug-induced lymphocyte stimulation test for various oral mesalamines in ulcerative colitis with mesalamine intolerance. *PLoS ONE*. 2025;20:e0334969.

23. Suzuki K, Kakuta Y, Naito T, et al. Genetic Background of Mesalamine-induced Fever and Diarrhea in Japanese Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis*. 2022;28:21–31.

24. Maillard M, Schwab M, Whirl-Carrillo M, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Thiopurine Dosing Based on TPMT and NUDT15 Genotypes: 2025 Update. *Clin Pharmacol Ther*. 2026;119:916–27.

25. Kakuta Y, Naito T, Onodera M, et al. NUDT15 R139C causes thiopurine-induced early severe hair loss and leukopenia in Japanese patients with IBD. *Pharmacogenomics J*. 2016;16:280–5.

26. Prioux-Klotz C, Nahon S, Amiot A, et al. Rate and Predictors of Mucosal Healing in Ulcerative Colitis Treated with Thiopurines: Results of a Multicentric Cohort Study. *Dig Dis Sci*. 2017;62:473–80.

Figures

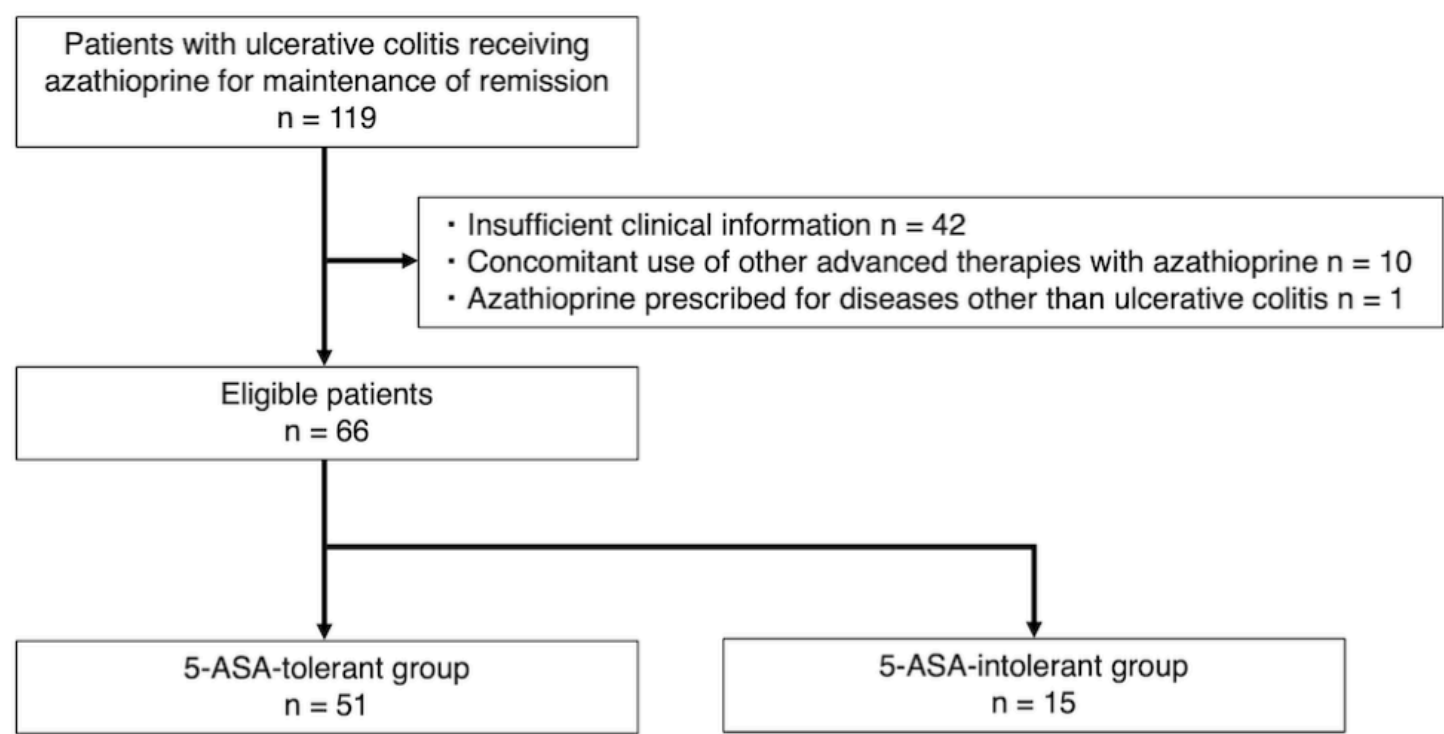


Figure 1

Flowchart of patient selection.

Among 119 patients with ulcerative colitis who received azathioprine for maintenance therapy, 53 were excluded because of insufficient clinical information (n = 42), concomitant use of advanced therapies with azathioprine (n = 10), or azathioprine use for diseases other than ulcerative colitis (n = 1). The remaining 66 patients were included in the study and categorized into the 5-ASA-tolerant group (n = 51) and the 5-ASA-intolerant group (n = 15).

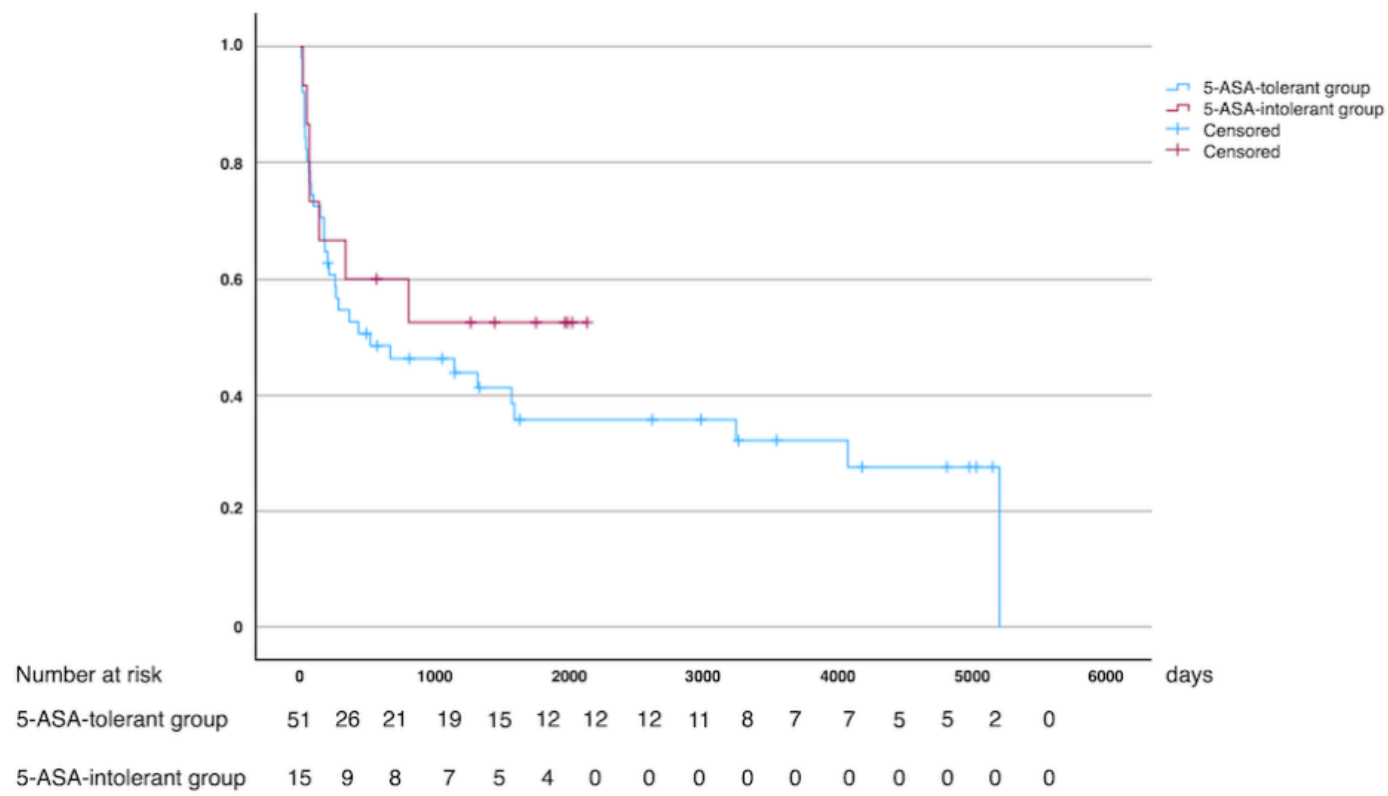


Figure 2

Kaplan–Meier analysis of azathioprine continuation according to 5-ASA intolerance status.

Kaplan–Meier curves showing cumulative azathioprine continuation rates in patients with ulcerative colitis stratified by 5-ASA intolerance status. The 1-year and 3-year continuation rates were 60.0% and 52.5%, respectively, in the 5-ASA-intolerant group and 52.6% and 46.3%, respectively, in the 5-ASA-tolerant group. No significant difference in azathioprine continuation was observed between the groups (log-rank p = 0.404). Tick marks indicate censored observations.

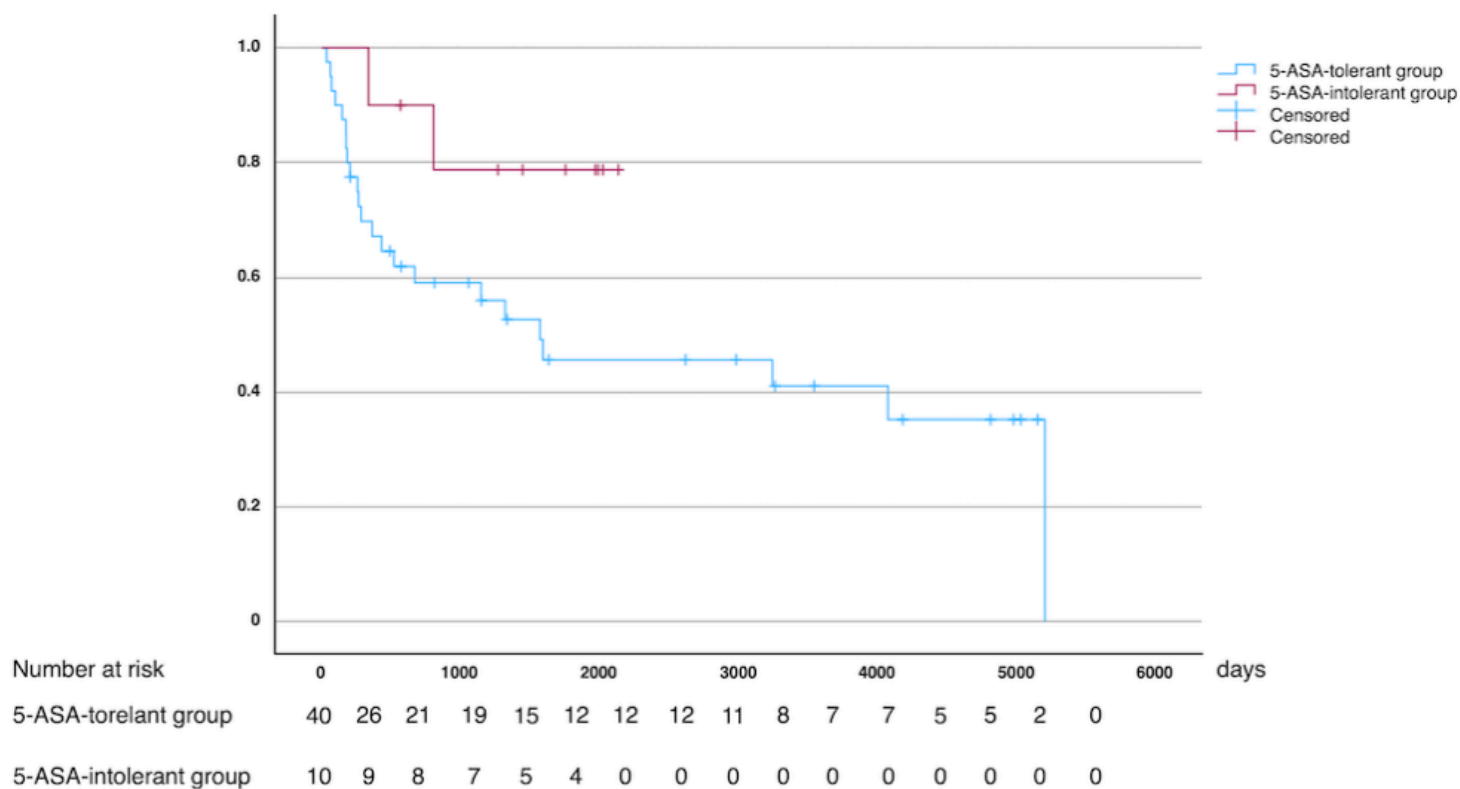


Figure 3

Kaplan–Meier analysis of azathioprine continuation after exclusion of discontinuations due to adverse events.

Kaplan–Meier curves showing cumulative azathioprine continuation rates in patients with ulcerative colitis by 5-ASA intolerance status after excluding patients who discontinued azathioprine because of adverse events. The 1-year and 3-year continuation rates were 90.0% and 78.8%, respectively, in the 5-ASA-intolerant group and 67.2% and 59.1%, respectively, in the 5-ASA-tolerant group. No significant difference in azathioprine continuation was observed between the groups (log-rank $p = 0.094$). Tick marks indicate censored observations.