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ORIGINAL ARTICLE

Retrospective Study

Azathioprine is essential following cyclosporine for patients with steroid-refractory ulcerative colitis

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Abstract

AIM: To evaluate long-term prognosis following cyclosporine treatment by examining the rate of surgery avoidance among cyclosporine responders.

METHODS: We retrospectively reviewed clinical records for 29 patients diagnosed with severe steroid-refractory ulcerative colitis in our hospital from August 1997 to August 2008 and treated with cyclosporine by continuous intravenous infusion. All patients were treated with intravenous corticosteroids for more than 5 d prior to cyclosporine therapy. Administration was continued for up to 21 d under serum monitoring to maintain cyclosporine levels between 400 and 600 ng/mL. Clinical activity was assessed before and after cyclosporine therapy using the clinical activity index score, with a reduction of $\geqslant 5$ considered to indicate a response. Among responders, we defined cases not requiring surgery for more than 5 years as exhibiting long-term efficacy of cyclosporine. Factors considered to be possibly predictive of long-term efficacy of cyclosporine were sex, age, disease duration, clinical activity index score, C-reactive protein level, hemoglobin level, disease extent, endoscopic findings, and clinical course.

RESULTS: Cyclosporine was not discontinued due to side effects in any patient. Nineteen (65.5%) of 29 patients were considered responders. A statistically significant ($P = 0.004$) inverse association was observed between an endoscopic finding of "mucosal bleeding" and responsive cases. Fifteen (9 males, 6 females) of these 19 patients were followed for 5 years or more, of whom 9 (60%) exhibited long-term

efficacy of cyclosporine. Of the 10 non-responders, 9 (90%) underwent surgery within 6 mo of cyclosporine therapy. None of the following factors had a significant impact on the long-term efficacy of cyclosporine: sex, age, duration of disease, clinical activity index score, C-reactive protein level, hemoglobin level, extent of disease, endoscopic findings, or clinical course. In contrast, a significant association was observed for maintenance therapy with azathioprine after cyclosporine therapy (P = 0.0014).

CONCLUSION: Maintenance therapy with azathioprine might improve the long-term efficacy of continuously infused cyclosporine for severe steroid-refractory ulcerative colitis patients.

Key words: Ulcerative colitis; Cyclosporine; Maintenance therapy; Azathioprine; Long-term prognosis

Core tip: Cyclosporine is effective in avoiding emergency surgery in patients with severe steroid-refractory ulcerative colitis. However, few studies have evaluated long-term outcomes of cyclosporine therapy in Asia. This paper provides important information regarding the maintenance of steroid-free remission following cyclosporine therapy. Maintenance therapy with azathioprine improves the long-term efficacy of continuously infused cyclosporine in patients with severe steroid-refractory ulcerative colitis.

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INTRODUCTION

A proportion of patients with ulcerative colitis (UC) experience severe episodes that necessitate hospitalization at some point during the course of their disease[1]. This is a dangerous and potentially life-threatening clinical condition that requires intensive medical treatment and may lead to prompt colectomy in the case of treatment failure[2]. Most patients are conventionally treated with intravenous (Ⅳ) corticosteroids, but 30% to 40% of cases do not respond[3,4], and a substantial proportion of these require rescue therapy to avoid an urgent colectomy under poor conditions. Even when a patient manages to avoid colectomy, the role of rescue therapy on the long-term prognosis of the patient is unknown.

Lichtiger *et al*[5] reported the efficacy of Ⅳ cyclosporine (CyA), a fungal calcineurin inhibitor, in severe steroid-refractory ulcerative colitis, and several studies have since confirmed that Ⅳ CyA therapy avoids emergency total proctocolectomy in more than 60% of cases[4,6-8]. Meanwhile, the goal of UC treatment is not only the induction but also the maintenance of steroid-free remission, which improves quality of life and reduces the risk of future colectomy and cancer. Although several studies have reported the long-term outcome of CyA therapy in Western countries[7-12], few have evaluated this issue in Asia[13,14]. The need to investigate long-term outcomes following CyA therapy in Asia is warranted by possible differences in the pathogenesis and characteristics of inflammatory bowel disease (IBD) between Asian and Western countries[15].

Here, we evaluated the factors affecting long-term prognosis following CyA treatment by examining the rate of surgery avoidance among CyA responders at a hospital in Japan.

MATERIALS AND METHODS

Patients and treatment protocol

This retrospective study involved 29 consecutive UC patients treated with CyA by continuous Ⅳ infusion (CI) for severe UC that had been refractory to corticosteroid therapy in our hospital from August 1997 to August 2008 (Figure 1, Table 1). All patients were treated with Ⅳ corticosteroids for more than 5 d prior to CyA therapy. CyA was given by CI at an initial dose of 2 mg/kg per day for a maximum of 3 wk. Blood levels during infusion were measured daily by monoclonal assay, and dosage was adjusted between 2 and 4 mg/kg per day to maintain CyA levels between 400 and 600 ng/mL. Conventional medication was continued and steroid dose was tapered when the DAI score decreased to remission levels (4 or less). The general condition of patients was evaluated, and the number of daily bowel movements, presence of abdominal pain and tenderness, use of anti-diarrheals, blood in stools, general well-being, fecal incontinence, and nocturnal diarrhea were scored according to the clinical activity index (CAI) by physicians[16].

Cyclosporine responders and follow-up

CAI score assessment and blood tests were conducted before and after CyA therapy. For CAI scores, patients with a score reduction of $\geqslant$ 5 were considered "responders". Following CyA therapy, responders continued treatment with oral CyA, oral prednisolone (PSL), leukocytapheresis (LCAP), tacrolimus (TAC), and azathioprine (AZA). Oral CyA was administered for up to 3 mo. Oral prednisolone was tapered and stopped according to patient condition. AZA was started at 25 mg/d, and, if severe adverse effects did not occur, was increased in 25-mg increments to a maximum of 100 mg/d. 5-ASA and AZA were continued as long as possible. Complete blood counts and levels of aminotransferases, amylase, creatinine, and C-reactive protein (CRP) were analyzed before and 1, 2, and 4 wk after CyA therapy, and every month thereafter.

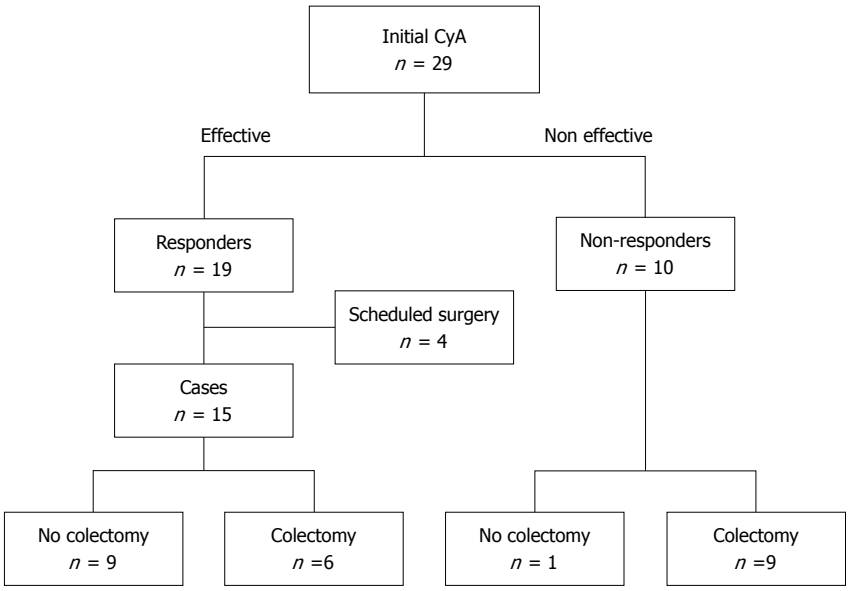

Figure 1 Clinical course of 29 patients up to 5 years after GI-CyA therapy. Patients with a CAI score reduction of ⩾ 5 were considered "responders". The term "no colectomy" includes all patients who were not treated surgically for up to 5 years. CAI: Clinical activity index.

Table 1 Predictive factors for cyclosporine response

	Responders (*n* = 19)	Non-responders (*n* = 10)	*P* value
Clinical factor			
Fever (℃) ⩾ 38.5: < 38.5	10:9	6:4	*P* = 1.000 NS
Hb (g/dL)	10.6	9.8	*P* = 0.317 NS
CAI score	14.6	15.0	*P* = 0.575 NS
Age (yr)	32.8	34.3	*P* = 0.804 NS
Duration (mo)	67.7	57.9	*P* = 0.703 NS
CRP (mg/dL)	6.5	3.6	*P* = 0.104 NS
Endoscopic finding			
Endoscopic index	9.9	10	*P* = 0.819 NS
Deep or geographical ulcer	89.5% (17:2)	50% (5:5)	*P* = 0.111 NS
Mucosal bleeding	42.1% (8:11)	100% (10:0)	*P* = 0.004
Poor extensibility	31.6% (6:13)	70% (7:3)	*P* = 0.064 NS
Pus-like discharge	89.5% (17:2)	90% (9:1)	*P* = 1.000 NS

UC: Ulcerative colitis; CAI: Clinical activity index; CRP: C-reactive protein.

Table 2 Demographic data and clinical features of responders

	Total (*n* = 15)
Sex (patient number)	
Male	9
Female	6
Age at onset (yr; mean ± SE)	26.2 ± 3.5
Age at CyA treatment (yr; mean ± SE)	30.5 ± 3.8
Duration of UC (months; mean ± SE)	62.3 ± 19.2
Disease extent (patient number)	
Pancolitis	12
Left-sided colitis	3
Clinical course (patient number)	
Relapse-remitting	11
Chronic continuous	3
Acute fulminating	1
Initial attack	0

Factors considered to be possibly predictive of long-term efficacy of CyA were sex, age, disease duration, CAI score, CRP level, hemoglobin (Hb) level, disease extent, endoscopic findings, and clinical course. Study endpoint was proctocolectomy, and long-term outcome was evaluated by Kaplan-Meier survival analysis. We defined the long-term efficacy of CyA as the avoidance of colectomy for 5 years after CyA therapy.

Statistical analysis

Continuous data were compared using the Mann-Whitney test, and categorical data using the χ^2 test. Colectomy avoidance rate was estimated by the Kaplan-Meier method. Multivariate analyses were performed by multiple logistic regression. Data were analyzed using JMP® 10 (SAS Institute Inc., Cary, NC, United States) statistical analysis software and standard binomial proportion analyses. Confidence intervals and *P*-values were calculated using the standard *t*-test. Statistical significance was taken as $P < 0.05$.

RESULTS

Response to CyA treatment

CyA therapy was not discontinued due to side effects in any patient. Of the 29 UC patients treated with CyA, 19 (65.5%) were considered responders (Figure 1). On comparison, clinical factors such as the presence or absence of high fever, Hb, CAI score, age at the beginning of CyA treatment, duration of UC, and CRP did not statistically differ between the groups (Table 1). Regarding endoscopic findings, a statistically significant inverse association was observed between "mucosal bleeding" and responsive cases (Table 1). Four of the 19 CyA responders underwent

Table 3 Clinical data and outcome of responders to CyA therapy

Case No.	Age	Sex	Duration of UC	Disease extent	Endoscopic findings[1]			Clinical factors[1]			Outcome
					Poor extensibility	Deep ulcer	Mucosal bleeding	CAI	CRP	Hgb	
1	23	F	24M	Pancolitis	(-)	(+)	(-)	17	3.2	9.3	Operation at 4M
2	37	M	67M	Pancolitis	(-)	(+)	(+)	16	1.5	10.9	No operation
3	23	M	44M	Pancolitis	(-)	(+)	(-)	15	7.0	13.7	Operation at 1Y, 4M
4	32	F	77M	Pancolitis	(-)	(-)	(-)	14	1.3	8.6	Operation at 2Y, 10M
5	31	F	26M	Pancolitis	(-)	(-)	(-)	13	12.8	13.4	No operation
6	9	F	13M	Pancolitis	(-)	(-)	(-)	15	12.5	13.2	Operation at 5M
7	16	M	79M	Lt-sided colitis	(-)	(+)	(-)	15	12.8	11.9	Operation at 1M
8	16	F	1M	Pancolitis	(-)	(+)	(-)	17	8.1	8.7	No operation
9	31	M	65M	Lt-sided colitis	(-)	(+)	(-)	12	14.7	10.0	No operation
10	21	M	22M	Pancolitis	(-)	(+)	(-)	17	6.4	11.8	No operation
11	49	M	27M	Lt-sided colitis	(+)	(+)	(+)	13	13.7	7.8	No operation
12	29	F	47M	Pancolitis	(+)	(+)	(+)	13	4.6	8.0	No operation
13	61	M	9M	Pancolitis	(+)	(+)	(-)	15	0.4	10.7	No operation
14	54	M	300M	Pancolitis	(+)	(+)	(+)	12	7.1	13.5	No operation
15	26	M	134M	Pancolitis	(+)	(+)	(+)	18	4.1	10.9	Operation at 2M

[1]At beginning of cyclosporine treatment; M: Months; Y: Years. CAI: Clinical activity index; CRP: C-reactive protein; UC: Ulcerative colitis.

Table 4 Following therapies for initial cyclosporine responders

Maintenance therapy	Total (n = 15)	Outcome	
		Colectomy (n = 6)	No colectomy (n = 9)
Without azathioprine			
PSL	1	1	
5-ASA+PSL	4	3	1
PSL+neoral	1	1	
5-AZA+PSL+neoral+LCAP	1	1	
With azathioprine			
5-ASA+PSL+AZA	1		1
5-ASA+PSL+neoral+AZA	5		5
5-ASA+PSL+neoral+TAC+AZA	1		1
5-ASA+PSL+neoral+LCAP+AZA	1		1

PSL: Prednisolone; LCAP: Leukocytapheresis; AZA: Azathioprine; LCAP: Leukocytapheresis; TAC: Tacrolimus.

scheduled colectomy, leaving 15 patients (9 males, 6 females) for inclusion in this study (Figure 1) and follow-up for 5 years. Demographic data and clinical features of these 15 patients are shown in Table 2, and clinical factors and endoscopic findings at the beginning of CyA treatment and outcomes in Table 3.

Follow-up therapies and outcomes of responders

After CI-CyA treatment, the 15 responders received additional treatment as follows: PSL alone (n = 1); 5-ASA and PSL (n= 4); PSL and neoral (n = 1); 5-ASA, PSL, neural, and LCAP (n =1); 5-ASA, PSL, and AZA (n = 1); 5-ASA, PSL, neoral, and AZA (n = 5); 5-ASA, PSL, neoral, TAC, and AZA (n = 1); and 5-ASA, PSL, neoral, LCAP, and AZA (n = 1) (Table 4). Nine (60%) of the 15 responders showed long-term efficacy of CyA (Figure 1, Table 3). The six remaining responders underwent colectomy (pan-proctocolectomy and ileostomy) within a short period (mean duration 9.75 mo, range 2-34 mo) (Table 3).

Table 5 Demographic data and clinical features of patients according to long-term prognosis

	Colectomy (n = 6)	No colectomy (n = 9)	P value
Male:Female (patient no.)	2:4	6:3	P = 0.315 NS
Age at onset (yr; mean ± SE)	17.0 ± 2.8	32.3 ± 4.6	P = 0.063 NS
Age at CyA treatment (yr; mean ± SE)	21.5 ± 3.3	36.6 ± 5.1	P = 0.099 NS
Duration of UC (mo; mean ± SE)	61.8 ± 18.1	62.7 ± 30.6	P = 0.982 NS
CAI score pre-CyA (mean ± SE)	15.7 ± 0.6	14.2 ± 0.7	P = 0.164 NS
CAI score post-CyA (mean ± SE)	5.0 ± 1.0	5.6 ± 1.2	P = 0.732 NS
CRP pre-CyA (mean ± SE)	6.8 ± 2.0	7.7 ± 1.7	P = 0.726 NS
Hb (mean ± SE)	11.3 ± 0.8	10.5 ± 0.7	P = 0.520 NS
Disease extent (patient No.)			
Pancolitis: Lt-sided colitis	5:1	7:2	P = 1.000 NS
Clinical course (patient No.)			P = 0.446 NS
Relapse-remitting	4	7	
Chronic continuous	1	2	
Acute fulminating	1	0	
Initial attack	0	0	
Endoscopic findings			
Poor extensibility (+):(-)	1:5	4:5	P = 0.584 NS
Deep ulcer (+):(-)	4:2	8:1	P = 0.523 NS
Mucosal bleeding (+):(-)	1:5	4:5	P = 0.580 NS

CAI: Clinical activity index; CRP: C-reactive protein; UC: Ulcerative colitis.

Clinical factors and endoscopic findings predictive of long-term prognosis

We evaluated each clinical factor as a predictor of long-term prognosis by comparison between patients with and without colectomy. Clinical data, such as median age, duration of UC, CAI score, CRP level, Hb level, and clinical course showed no statistically significant difference between the two groups (Table 5). Furthermore, no predictive endoscopic findings showed a significant correlation with long-term prognosis. Consequently, no clinical factors or endoscopic findings were predictive of long-term prognosis (Table 5).

Table 6 Outcome according to each following therapy after cyclosporine

	Colectomy (*n* = 6)	No colectomy (*n* = 9)	*P* value
Maintenance therapy			
PSL	6	9	
LCAP	1	0	*P* = 0.4000 NS
5-ASA	4	9	*P* = 0.1429 NS
Neoral	2	7	*P* = 0.1357 NS
AZA	0	8	*P* = 0.0014

PSL: Prednisolone; LCAP: Leukocytapheresis; AZA: Azathioprine.

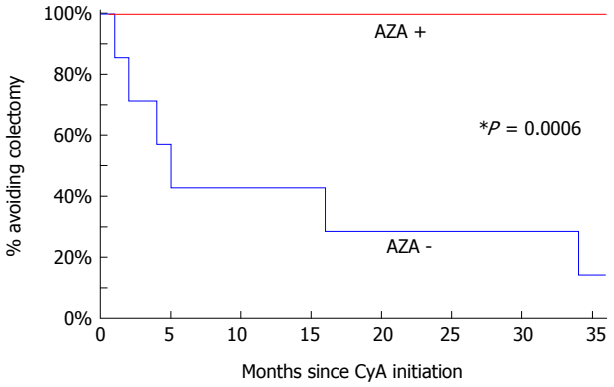

Figure 2 Kaplan-Meier analyses of avoidance of colectomy versus time for responding patients with or without azathioprine treatment (overall, *n* = 15, with azathioprine, *n* = 8, and without azathioprine, *n* = 7, respectively). *P* = 0.006 *vs* no AZA treatment by the log-rank test. AZA: Azathioprine.

Effect of subsequent therapies on long-term prognosis

After CI-CyA treatment, 8 of the 15 responders were treated with AZA in conjunction with other conventional therapies (Tables 4 and 6). All eight patients treated with AZA achieved long-term remission. In contrast, only one of the nine non-colectomy patients was not treated with AZA (Tables 4 and 6). A significant association was observed between maintenance therapy with AZA and long-term effectiveness after CyA therapy ($P = 0.0014$) (Table 6). We verified the necessity of AZA after CyA for maintenance of remission by Kaplan-Meier analysis of avoidance of colectomy versus time since CyA patients started treatment with and without AZA (Figure 2) ($P = 0.0006$).

Complications of therapy

Patients were carefully monitored for any symptoms of opportunistic infection. One patient was identified as cytomegalovirus (CMV) antigenemia-positive, but CyA therapy was continued with ganciclovir (GCV) injection therapy. Although none of the patients discontinued CyA therapy due to adverse events, most experienced minor adverse events during CyA therapy. The most common complication was hypertension, but all cases were treated with antihypertensive agents or observation. Similarly, a proportion of patients experienced tremors, candidiasis, hyperkalemia, nausea, headaches, and hyperglycemia during CyA therapy, but the therapy could be continued in all affected patients following a reduction in CyA dose. All complications were reversible and all patients completely recovered after CyA therapy.

With regard to maintenance therapy with 5-ASA in initial CyA responders, we could not use 5-ASA in three patients due to allergy to 5-ASA in two and nausea in one. All three patients eventually underwent colectomy. Patients treated with AZA complained of adverse events more frequently than those with other therapies. A small proportion of patients treated with AZA required a reduction in AZA dose due to leucopenia and liver dysfunction, which then immediately returned to normal. However, AZA was not withdrawn in any of these patients. Overall, no patients had to stop maintenance therapy due to side effects.

DISCUSSION

The primary goal of this study was to evaluate the long-term prognosis of patients with UC after CyA treatment by examining the surgery avoidance rate among CyA responders. CRP titer and endoscopic findings were significantly associated with short-term response. However, sex, age, duration of disease, CAI score, CRP level, Hb level, extent of disease, endoscopic findings, and clinical course were not significantly correlated with long-term effectiveness. The only factor showing a significant association with the long-term efficacy of CyA was post-CyA maintenance therapy with AZA ($P = 0.0014$). These findings indicate that administration of AZA after CI-CyA therapy might provide long-term efficacy for severe steroid-refractory UC patients in Japan.

Induction therapy with CyA for severe steroid-refractory UC has provided an effective medical alternative to patients who previously faced only surgical options. Controlled[4] and uncontrolled trials[5] have established the efficacy of short-term CyA as a "rescue therapy" in severe UC. In our study, 29 patients with severe steroid-refractory UC were treated with CyA, of whom 19 (65.5%) were identified as responders. CyA therapy could be continued for all patients despite the presence of a number of side effects. The greatest concern in treatment with CyA is opportunistic infections[17]. In our study, one patient developed CMV infection, but CyA could be continued with concomitant use of the anti-virus agent GCV. We therefore recommend careful monitoring during CyA therapy to ensure patient safety; in our hospital we have established a system in which serum CyA levels are assayed on the same day as samples are obtained, with CyA dosage then being adjusted accordingly.

CyA, on a short-term basis, can prevent colectomy in a substantial proportion of patients with severe steroid-refractory UC. This benefit appears limited on a long-term basis however, with up to 50% of responders losing their colon within 9 mo[18]. In our study, 6 (40%) of the 15 CyA responders consequently underwent colectomy within 34 mo. Immunosuppressive therapy with AZA or

6-mercaptopurine has been used in steroid-dependent UC patients who failed maintenance therapy with 5-ASA[19,20]. In our study, a significant association was observed between maintenance therapy with AZA and long-term effectiveness following CyA therapy, and AZA was the only factor that significantly correlated with long-term effectiveness. Indeed, all patients who received AZA as maintenance therapy avoided colectomy. Our findings indicate that once remission is achieved using CyA, maintenance therapy with AZA is critical, and we strongly recommend the addition of AZA to conventional therapies for CyA responders. As treatment with AZA may take 2 or 3 mo to achieve its full efficacy[21], we initiated AZA while the patient was still on cyclosporine and steroids were being tapered.

The toxicity of immunosuppressive agents includes bone marrow suppression, particularly leukopenia, which is usually dose-dependent. As leukopenia most frequently occurs within the first few weeks to months of use, complete blood counts should be measured more frequently during the early period, although late bone marrow suppression may occur. We measured complete blood cell counts at 1, 2, and 4 wk, and then every month after the initiation of AZA. The risk of opportunistic infections was approximately three-fold higher in IBD patients who used AZA[22]. Infections tend to be more serious in patients with lower absolute lymphocyte counts or leukopenia. The frequency of liver abnormalities varies between 2% and 17% of patients[23], with a proportion of patients experiencing an increase in amylase[24,25]. The mechanism of AZA-induced pancreatic damage, in the form of either asymptomatic elevation in serum amylase or lipase, or overt acute pancreatitis, is still not clear. Patients treated with AZA require regular biochemical testing to exclude potential liver dysfunction or pancreatotoxicity. We conducted blood tests including aminotransferases and amylase, as well as complete blood cell counts. In this study, none of the patients had to stop AZA during maintenance therapy due to adverse effects.

The question of when AZA treatment should be stopped following CyA treatment is controversial. Discontinuation might be associated with UC relapse, while continuation might increase the incidence of side effects. An answer to this question requires a risk-to-benefit ratio analysis with consideration to both the relapse of UC after AZA discontinuation and the risk of prolonged AZA treatment. Bouhnik *et al*[26] reported that CD patients treated with AZA maintained remission for at least 4 years, while Kobayashi *et al*[14] reported that all seven UC patients in their study who stopped AZA during remission after CyA treatment experienced relapse, with six requiring surgery. On the other hand, follow-up data from renal transplant recipients suggest an increased risk of malignancy with prolonged use of AZA, such as skin cancers, non-Hodgkin's lymphoma, and other solid tumors[27,28]. In contrast, Connell *et al*[29] observed no increased risk of malignancy in 755 patients with inflammatory bowel disease followed for a median of nine years from the start of AZA treatment. Furthermore, Fraser *et al*[30] also reported no increased risk of malignancy during 6.9 years of follow-up in IBD patients treated with AZA.

Other than AZA, we also used 5-ASA as maintenance therapy after CyA treatment. 5-ASA is effective for maintenance of remission in UC[31-35], and was administered to all our present UC patients as maintenance therapy due to its safety. However, it was stopped in 3 of 15 patients due to allergy or nausea. These three patients subsequently required colectomy. Although our efficacy data for 5-ASA did not show statistical significance, we nevertheless recommend 5-ASA in addition to AZA as maintenance therapy after CyA.

Several limitations of this study warrant mentioning. First, the number of included patients was small and they were studied retrospectively. Patients were not randomly selected to take AZA; rather, administration was at the discretion of the attending physician. Second, discontinuation of AZA was not required in any of our patients, suggesting that they may not have required this drug. To confirm the need for AZA and the appropriate duration of administration in maintenance therapy following CyA treatment, a prospective randomized controlled trial is required.

In conclusion, treatment with AZA after CI-CyA therapy might provide long-term effectiveness in Japanese patients with severe steroid-refractory UC. Additional studies are required to determine the optimum timing of AZA cessation in patients who have been stable under maintenance therapy with AZA following CI-CyA.

COMMENTS

Background

Cyclosporine is effective in avoiding emergency surgery in patients with severe steroid-refractory ulcerative colitis. However, few studies have evaluated long-term outcomes of cyclosporine therapy in Asia.

Research frontiers

How to improve long-term prognosis following cyclosporine treatment for ulcerative colitis patients.

Innovations and breakthroughs

Maintenance therapy with azathioprine might improve the long-term efficacy of continuously infused cyclosporine for severe steroid-refractory ulcerative colitis patients.

Applications

For severe steroid-refractory ulcerative colitis patients, we recommend the administration of azathioprine in addition to conventional therapies for cyclosporine responders.

Terminology

Cyclosporine is an inhibitor of calcineurin activation and interrupts the cellular immune response by blocking interleukin 2 production by T cells. Azathioprine, an immunomodulator, was initially used clinically in the management of childhood leukemia and organ transplantation.

Peer review

This study shows the effect of azathioprine maintenance therapy on long-term remission in steroid refractory ulcerative colitis patients rescued with cyclosporine. The information in this study may be a useful addition to the existing literature on this topic.

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