



Long-term outcome in patients with ulcerative colitis treated with intravenous cyclosporine A is determined by previous exposure to thiopurines

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Abstract

Background and aim: Rescue therapy with intravenous cyclosporine A (CsA) helps to avoid colectomy in a substantial proportion of patients with severe ulcerative colitis (UC) but the impact on long-term outcome remains unclear. Therefore, we aimed to define predictive factors for colectomy in patients treated with intravenous CsA for severely active UC.

Methods: A retrospective, single-center study with a minimum follow-up of 18 months was performed.

Results: A total of 64 patients were evaluable (median age 33 years [range 17–80 years], female 54.7%). Median intravenous CsA dose was 4 mg/kg/day (range 2–5 mg/kg/day). After a median follow-up of 65 months (range 2–160 months), 19 patients (29.7%) underwent colectomy, 15 within 18 months. Of the various baseline parameters tested, only previous non-response to thiopurine treatment ($p=0.006$) was associated with an increased risk of colectomy. During 18 months follow-up, thiopurine-naïve patients receiving thiopurine maintenance therapy after intravenous CsA (32/64, 50.0%) underwent colectomy in 12.5% of cases. The colectomy rate was 27.3% among 22 patients previously non-responsive to thiopurines who continued treatment after intravenous CsA, compared to 50.0% in the 10 patients who discontinued thiopurines prior to intravenous CsA or who never received thiopurines ($p=0.037$).

Conclusions: The long-term colectomy rate after intravenous CsA in patients with severely active UC was relatively low in our series compared to the literature. Concomitant treatment with thiopurines was the only predictor for a reduced risk of colectomy.

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1. Introduction

Approximately 15% of patients with ulcerative colitis (UC) experience a severe episode that necessitates hospitalization at some point during the course of their disease,¹ and the risk of colectomy approaches 30% in this potentially life-threatening condition.² Conventional treatment with intravenous (i.v.) corticosteroids fails in 20–30% of patients, such that a substantial proportion of patients require rescue therapy.^{2–5}

The calcineurin inhibitor cyclosporine A (CsA) is recommended for patients in whom UC is refractory to i.v. steroids.⁶ A small, randomized, double-blind, controlled trial has reported that i.v. CsA is superior to placebo for severe, steroid-refractory UC.⁷ Nine out of eleven patients (82%) treated with CsA at a dose of 4 mg/kg/day responded, compared to none of the patients receiving placebo. The efficacy of CsA in this setting was later substantiated by several case series indicating short-term response rates of between 56% and 92%.^{8–13} In a subsequent randomized, controlled study, CsA 2 mg/kg/day i.v. was shown to result in a similar short-term response rate (86%) to a dose of 4 mg/kg/day (84%), but was associated with less toxicity.¹⁴ The long-term outcome after CsA rescue therapy, however, appears less promising. In two series, 58% of 76 patients¹⁵ and 88% of 142 patients¹⁶ had to undergo colectomy during the following seven years.

Despite a relative scarcity of data, the thiopurines azathioprine and 6-mercaptopurine (6-MP) are broadly accepted for use as maintenance and steroid-sparing therapy in UC.⁶ Thiopurines are also recommended for maintenance of CsA-induced remission and to allow CsA withdrawal.⁶ Maintenance treatment with thiopurines in patients naïve to thiopurine therapy prior to i.v. CsA has been reported to be a positive predictive factor for long-term outcome after CsA treatment.¹⁶ However, predicting the course of severe UC is challenging and, in particular, prognostic factors for a response to CsA are needed urgently. Tachycardia, body temperature >37.5 °C, serum C-reactive protein (CRP) levels >45 mg/L, elevated band neutrophils, low serum albumin and severe endoscopic lesions have all been associated with failure of CsA treatment.^{17,18} More than eight bowel movements a day, or three to eight bowel movements a day coupled with a raised serum CRP concentration (>45 mg/L) at day 3 following hospital admission for severe colitis, were reported by Travis et al. to be highly predictive for colectomy in patients after a three-day course of i.v. steroids.⁵ Furthermore, the Fulminant score (i.e. number of bowel movements/day + 0.14 × CRP (mg/L)) identifies the majority of patients who require colectomy.¹⁹

If CsA rescue therapy fails, patients who undergo colectomy usually receive double or even triple immunosuppression, with a corresponding increase in the risk of perioperative infections and impaired wound healing compared to elective surgery.^{16,20} Morbidity may also escalate due to the numerous side effects associated with CsA.^{6,15,16} Thus, there is an urgent need to recognize prognostic factors that may help to identify at an early stage those patients who should be managed surgically instead of receiving CsA rescue therapy.

The aim of the present study was to define predictive factors for colectomy in our cohort of UC patients treated with i.v. CsA, in order to determine early which patients

should undergo surgery instead of rescue therapy with i.v. CsA.

2. Materials and methods

2.1. Patients and study design

We conducted a retrospective cohort study of patients who received i.v. CsA treatment for UC at our center between August 1993 and November 2005. Eligible patients were required to have severe UC according to the criteria of Truelove and Witts.²¹ A minimum follow-up of 18 months was necessary for inclusion, unless colectomy occurred sooner than 18 months. Each patient was included only once. A detailed chart review was performed for each patient, and laboratory results and clinical variables were assessed according to pre-specified criteria. If there had been no recent contact with a patient, he or she was followed up via telephone interview or via a questionnaire sent by regular mail.

2.2. Definitions

The most recent colonoscopy report prior to treatment with i.v. CsA was used to determine the extent of UC according to the Montreal classification.²² Left-sided colitis was defined as inflammation not exceeding the splenic flexure and extensive colitis spreading beyond the splenic flexure. Patients intolerant of, or unresponsive to, at least three months of thiopurine therapy (target dose range: azathioprine 2.0–2.5 mg/kg/day, 6-MP 1.0–1.5 mg/kg/day) were considered thiopurine failures. Baseline was immediately prior to i.v. CsA treatment. If more than one cycle of i.v. CsA treatment was given, the first cycle was always used as the reference point for baseline.

2.3. Study objective

The primary objective was to define predictive factors for colectomy in patients with severely active UC immediately prior to starting i.v. CsA treatment.

2.4. Evaluation

Comparisons between specific patient groups were performed using two well-established scoring systems for severe UC (the Travis Score⁵ and the Fulminant score¹⁹) in order to evaluate the prognostic potential of each scoring system. Comparisons were made between (a) patients requiring colectomy versus patients who did not require colectomy and (b) patients requiring colectomy or UC-related hospitalization and/or infliximab (IFX) therapy within 18 months (i.e. patients without sustained remission who required additional rescue therapy to avoid colectomy, but who were not yet designated for surgery) versus patients who did not require any of these interventions (i.e. patients who responded to CsA in the long term).

2.5. Endpoints

The primary endpoint was requirement for colectomy and/or death. Secondary endpoints included requirement for rescue therapy with IFX within 18 months after the start of i.v. CsA,

UC-related hospitalization within 18 months and the development of colorectal cancer.

2.6. Statistical analysis

Data are presented as frequencies, percentages and median values with ranges. Categorical data were compared using chi-square tests. For continuous data, the Mann–Whitney *U*-Test was used. Colectomy-free survival was analyzed with Kaplan–Meier estimates and the log rank test. Differences were considered significant if *p* was <0.05. SPSS (Version 13.0) was used for all statistical analyses.

3. Results

3.1. Study population

In total, 67 patients were identified. Two patients were excluded because data were incomplete and one patient was lost to follow-up, such that 64 patients were evaluated (Table 1). The median dose of i.v. CsA was 4 mg/kg/day (range 2–5 mg/kg/day), with 8 patients receiving 2 mg/kg/day, 5 patients receiving 3 mg/kg/day, 47 receiving 4 mg/kg/day and 4 receiving 5 mg/kg/day. The median duration of treatment was seven days (range 2–17 days). For six patients (9.4%) i.v. CsA was given for their first UC episode. Twenty-seven patients (42.2%) had previously been exposed to thiopurines prior to baseline i.v. CsA treatment, but had either failed to achieve or maintain remission, or were intolerant of thiopurine therapy.

3.2. Response to treatment

Patients were followed for a median of 65 months (range 2–160 months). Sixty patients (93.8%) were switched to oral CsA at a median dose of 4.4 mg/kg/day (range 2–5 mg/kg/day) for a median of 3.5 months (range 0–13 months). Four patients (6.2%) did not proceed to oral CsA either due to

unresponsiveness or intolerance of i.v. CsA. During follow-up, 19 patients (29.7%) had to undergo colectomy at a median of seven months (range 0–81 months) after baseline (Fig. 1). In one patient colectomy was indicated due to colorectal cancer; in all others the indication was treatment failure. During the minimum follow-up period of 18 months, 15 patients (23.4%) underwent colectomy. Forty-eight patients (75.0%) did not require colectomy within the first 18 months after starting CsA. Thirteen patients (13/48, 27.1%) experienced another severe exacerbation of UC within the first 18 months. Of these, eight patients were readmitted to hospital for a further course of corticosteroid therapy but did not progress to colectomy, and the remaining five patients received IFX 5 mg/kg/day, of whom one later required surgery and the other four avoided colectomy throughout the entire follow-up. After the first 18 months, seven more patients were admitted to hospital for IFX therapy due to recurring severe UC, of whom one patient had to undergo colectomy. Altogether, colectomy, UC-related hospitalization or IFX was required by 31 patients (48.4%) within the first 18 months after starting i.v. CsA.

The rate of colectomy in patients treated with i.v. CsA was similar before (11/37, 29.7%) and after (8/27 29.6%) the introduction of IFX for moderately to severely active UC at our unit in May 2002. Two patients (3.1%) died during follow-up, due to pulmonary embolism after colectomy and to suicide in a CsA responder approximately three years after starting i.v. CsA.

3.3. Predictive factors for colectomy

There were no significant differences between patients who did or did not require colectomy according to various baseline characteristics that reflect disease severity, including serum CRP, hemoglobin level, heart rate, number of bowel movements and smoking status (Table 1). Neither was any difference in outcome observed between patients experiencing a first episode of UC versus patients with established disease (*p*=0.46).

Table 1 Baseline characteristics. All continuous variables are shown as median (range).

	All patients (<i>n</i> =64)	Colectomy (<i>n</i> =19)	No colectomy (<i>n</i> =45)	<i>p</i> -value ^a
Female, <i>n</i> (%)	35 (54.7)	9 (47.4)	26 (57.8)	0.44
Age at diagnosis, years	30 (11–79)	37 (13–60)	26 (11–79)	0.18
Age at beginning of CsA, years	33 (17–80)	40 (18–60)	32 (17–80)	0.16
Duration of disease, years	3 (0–31)	4 (0–12)	3 (0–31)	0.17
Left-sided UC, <i>n</i> (%)	22 (34.4)	8 (42.1)	14 (31.1)	
Extensive UC, <i>n</i> (%)	42 (65.6)	11 (57.9)	31 (68.9)	
First attack of UC, <i>n</i> (%)	6 (9.4)	1 (5.3)	5 (11.1)	0.46
Smoker, <i>n</i> (%)	10 (15.6)	2 (10.5)	8 (17.8)	0.47
Ex-or non-smoker, <i>n</i> (%)	54 (84.4)	17 (89.5)	37 (82.2)	0.46
Baseline CRP (mg/L)	47 (10–293)	38 (10–186)	49 (10–293)	0.63
Heart rate (/min)	80 (58–120)	78 (58–106)	83 (60–120)	0.15
Weight (kg)	64.1 (42–108)	60 (48–108)	65.5 (42–93)	0.57
Thiopurine failure, <i>n</i> (%)	27 (42.2)	13 (68.4)	14 (31.1)	0.0058
Hemoglobin (g/dL)	10.6 (4.7–15.7)	11.2 (7.2–14.1)	10.5 (4.7–15.7)	0.58

^a Colectomy versus no colectomy.

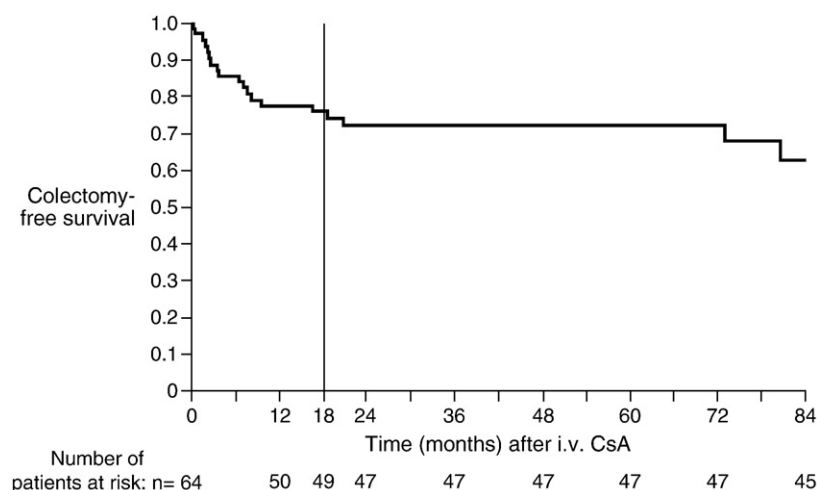


Figure 1 Colectomy-free survival after administration of i.v. CsA.

3.4. Influence of exposure to thiopurines on rate of colectomy

Of the 19 patients who underwent colectomy, 13 (68.4%) had been treatment failures under thiopurine therapy prior to starting i.v. CsA, compared to 6 (31.1%) who were thiopurine-naïve ($p=0.006$; Fig. 2).

Previous failure under thiopurines was also strongly predictive for non-responsiveness to i.v. CsA ($p<0.001$) when comparing patients requiring colectomy, IFX or hospitalization (thiopurine failures 20/31 [64.5%], thiopurine naïve 11/31 [35.5%]) to those without further intervention (thiopurine failures 7/33 [21.2%], thiopurine naïve 26/33 [78.8%]).

Within the 18-month minimum follow-up period, the 32 thiopurine-naïve patients who received thiopurine maintenance therapy after i.v. CsA underwent colectomy in four cases (12.5%). Among the 22 patients who had previously failed but continued to receive thiopurines after i.v. CsA, six (27.3%)

required colectomy compared to 50.0% of the 10 patients who had discontinued thiopurines prior to i.v. CsA or who had never received thiopurines ($p=0.037$).

Of those 37 patients who were naïve to thiopurines before receiving i.v. Cyclosporine A, two patients received infliximab and three required corticosteroids within 18 months after the start with CsA. Of the 27 patients who were failures to thiopurines, three patients received IFX and five patients were treated with another course of corticosteroids.

3.5. Performance of Fulminant score¹⁹ and Travis score⁵ to predict colectomy

At baseline, the median Fulminant score was 16.4 (range 4.4–48.4). Scores did not differ between patients who required colectomy (median 16.7, range 4.4–43.1) or did not require colectomy (median 16.1, range 5–48.8; $p=0.88$) or between patients who required colectomy, IFX or hospitalization

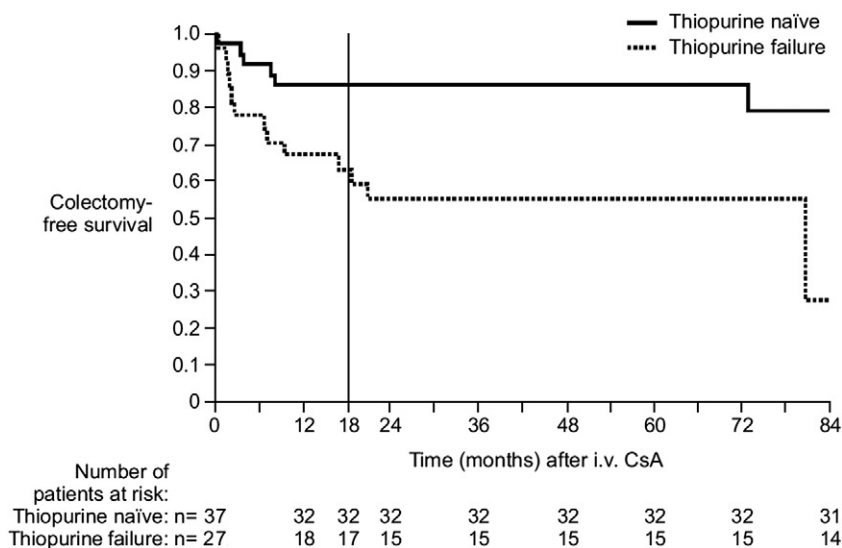


Figure 2 Colectomy-free survival after administration of i.v. CsA according to previous exposure to thiopurines.

(median 16.4, range 4.4–43.1) and those who did not (median 16.4, range 6.1–48.8; $p=0.83$). Similarly, baseline scores according to Travis et al. did not discriminate between patients with different outcomes (Table 2).

3.6. Side effects

Twenty-nine patients (45.3%) reported one or more side effects, of which neurotoxic complications including paraesthesia and tremor were the most frequent. Other side effects included nephrotoxicity (3/64, 4.7%) and arterial hypertension (2/64, 3.1%). One patient had an anaphylactic reaction while on i.v. CsA and one patient experienced a cytomegalovirus infection while receiving oral CsA. There were no other cases of severe opportunistic infections.

4. Discussion

CsA can prevent colectomy in a substantial proportion of patients with severely active UC on a short-term basis. Its long-term efficacy, however, appears limited since it has been reported that up to 50% of patients lose their colon within the first year.¹⁸ About 30% of the patients included in our study required surgery after a median follow-up of 65 months, which is one of the lowest rates of colectomy described in the literature.^{11,12,15,16} In contrast, Campbell et al. described results from 76 patients receiving CsA, of whom 65% and 90% relapsed after one and three years, respectively.¹⁵ After seven years, 58% of patients required colectomy, while Moskovitz et al.¹⁶ reported colectomy in 88% of patients after a similar follow-up period.

The low rate of colectomy observed here may reflect a defensive attitude to saving the patients' colon for as long as possible and reasonable. Nearly 80% of all colectomies had to be performed within the first 18 months after starting of i.v.

CsA. Another 13 patients (20.3%) received IFX or required rehospitalization because of recurring severe UC, with one patient undergoing colectomy, and an additional four colectomies performed subsequently. This finding supports the general approach of initiating a further course of intensive medical treatment in short-term responders to CsA, which may be a help to prevent colectomy in the long term. However, it should be pointed out that the introduction of IFX for severe UC at our unit did not appear to influence the rate of colectomy.

The primary aim of this study was to define baseline clinical and laboratory characteristics that would predict the outcome of patients treated with i.v. CsA. Patients who failed to respond to thiopurine therapy prior to the administration of i.v. CsA were less likely to respond to CsA.

The follow-up time of thiopurine naïve patients and thiopurine failures does not differ significantly (thiopurine naïve patients: median 70 months (range: 17–160), thiopurine failures: median 52 months (range 2–150), $p=0.22$). It demonstrates, that the better outcome of thiopurine naïve patients was not influenced by a shorter follow-time. The impact of the thiopurine status on the outcome became even more apparent when patients requiring hospitalization or IFX within 18 months were grouped with patients requiring colectomy. The risk for colectomy appeared highest in patients who had already received thiopurines prior to i.v. CsA but who subsequently discontinued due to unresponsiveness or intolerance, and in patients who had never received thiopurines. The patients who received thiopurines for the first time after i.v. CsA experienced the greatest benefit from i.v. CsA, with the lowest rate of colectomy. These findings confirm those of other investigators who demonstrated reduced risk for surgery in patients receiving concomitant treatment with thiopurines. In a French study, patients receiving thiopurines had a lower requirement for colectomy than the individuals without subsequent thiopurine therapy (18.8% versus 100%,

Table 2 Travis and Fulminant scores according to the presence or absence of colectomy (Cx) and the presence or absence of colectomy, infliximab and hospitalization (Cx/IFX/hosp).

Travis scoring system			
	Cx	Cx	p-value
>8 BM/day, n (%)	10 (52.6)	20 (44.4)	0.60
3–8 BM/day and CRP>45 mg/L, n (%)	3 (15.8)	12 (26.7)	0.33
	Cx/IFX/hosp	No Cx/IFX/hosp	p-value
>8 BM/day, n (%)	14 (45.2)	16 (48.5)	0.70
3–8 BM/day and CRP >45 mg/L, n (%)	8 (25.8)	7 (21.2)	0.71
Fulminant scoring system			
	Cx	Cx	p-value
Median (range)	16.7 (4.4–43.1)	16.1 (5.0–48.8)	0.88
	Cx/IFX/hosp	No Cx/IFX/hosp	p-value
Median (range)	16.4 (4.4–43.1)	16.4 (6.1–48.8)	0.83

BM, bowel movements; CRP, C-reactive protein.

$p=0.007$).²³ The high rate of concomitant thiopurine therapy in our population (84%) is the most likely explanation for the low rate of colectomy observed. Only 12.5% of thiopurine-naïve patients who started thiopurines after a short-term response to CsA progressed to colectomy. Our results support the European Crohn's and Colitis Organisation (ECCO) guidelines, which suggest continuing treatment with CsA until immunomodulator therapy is established.⁶

Our approach of using the Fulminant and the Travis scoring systems to assess potential predictors for colectomy in the setting of i.v. CsA for patients with severe active UC is novel. The Fulminant scoring system originates from a Swedish study of 97 patients with moderate to severe active UC treated with i.v. steroids.¹⁹ Using the formula 'number of bowel movements/day + $0.14 \times \text{CRP (mg/L)}$ ', there is a high chance that patients requiring colectomy will be identified early (i.e. those patients who exceed the cut-off score of 8 points on the third day of steroid treatment). The Travis score has been evaluated in a prospective study of patients with severe UC receiving i.v. hydrocortisone, followed by i.v. CsA in some incomplete responders.⁵ According to the Travis scoring system, 85% of patients with more than eight bowel movements a day, or with three to eight bowel movements a day and $\text{CRP} > 45 \text{ mg/L}$ on the third day of steroid therapy, will require colectomy on the same admission. In our study, both indices were applied immediately before the first course of i.v. CsA, but this was after a variable period of steroid treatment. Neither scoring system identified patients at increased risk for colectomy or for colectomy, IFX rescue therapy or hospitalization. It could be speculated that the baseline inflammatory load is of lower predictive value than individual tolerance of, and responsiveness to, combined immunosuppression with CsA and thiopurines.

Toxicity is considered to be the major disadvantage of CsA.^{6,15} In our cohort, one or more adverse effect was recorded in 45% of patients, with neurotoxic effects being the most frequent. Nephrotoxicity, arterial hypertension and opportunistic infections were rare, despite the fact that most patients were receiving double or triple immunosuppression. All side effects were reversible and none was life threatening. Neither of the deaths occurring during follow-up was considered related to CsA treatment. Therefore, in our experience, CsA appears to be reasonably safe.

5. Conclusions

The current study provides evidence that i.v. CsA effectively helps to avoid long-term colectomy in patients with severe active UC who have previously not received thiopurines. However, there is an urgent need for alternative treatments, particularly for patients who do not respond to immunosuppressants. The optimum sequence or combination of therapies to minimize the risk of a severe flare-up of UC remains to be determined.

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