Clinical Response and Complications are not Associated with Drug Levels in Patients with Severe Ulcerative Colitis on IV Cyclosporine Induction Therapy

Parita Patel, MD,* Andres Yarur, MD,[†] Sushila Dalal, MD,[‡] Atsushi Sakuraba, MD, PhD,[‡] David T. Rubin, MD,[‡] Stephen B. Hanauer, MD,[§] Ira Hanan, MD,[‡] Laura H. Raffals, MD,[¶] Russell D. Cohen, MD,[‡] and Joel Pekow, MD,^{‡,*}

Background: IV ciclosporin therapy is effective in steroid-refractory ulcerative colitis. The optimal drug level to achieve response and minimize complications during induction therapy is not known.

Aim: The primary aim was to evaluate if serum ciclosporin drug levels are associated with increased risk of colectomy within 90 days of hospitalization. Secondary aims were to determine if ciclosporin levels are associated with avoidance of colectomy at 7 and 30 days, if ciclosporin levels are associated with drug-related and postoperative complications, and if patient-specific factors are associated with response to ciclosporin.

Methods: We conducted a retrospective analysis of 81 hospitalized patients with steroid-refractory ulcerative colitis treated with ciclosporin. Risk factors for colectomy within 7, 30, and 90 days, medication-specific and postoperative complications were compared by first, mean, and peak ciclosporin level during IV induction therapy.

Results: There were 47 patients (58%) who underwent surgery. There were no differences between initial, mean, and peak ciclosporin levels among responders and nonresponders and treatment-related or postoperative complications. Responders within 90 days had lower C-reactive-protein levels (20mg/L vs. 38mg/L, $P = 0.01$), lower serum albumin concentrations (3.4g/dL vs. 3.7g/dL, $P = 0.03$), and higher rates of kidney injury (50% vs 17%, $P = 0.002$).

Conclusion: Initial, mean, and peak serum levels of ciclosporin did not correlate with response or toxicity. However, C-reactive-protein levels and kidney injury may be helpful in predicting clinical response to ciclosporin.

Key Words: ulcerative colitis, ciclosporin, complications, drug levels

INTRODUCTION

Fifteen to 50% of patients with ulcerative colitis (UC) will experience a severe flare requiring hospitalization during the course of their disease.^{1,2} Although treatment with intravenous

(IV) corticosteroids is effective in the management of severe UC,^{3,4} approximately 25%–40% of patients do not respond to corticosteroids.^{5–7} In corticosteroid-refractory patients with severe UC, previous data support the use of medical therapy with either infliximab or calcineurin inhibitors (ciclosporin and tacrolimus) as a “salvage” strategy to prevent colectomy.^{1,8–15} Whereas randomized control trials and a network meta-analysis demonstrated equivalence of these therapies in severe UC,^{6,16,17} there are limited data regarding predictive factors of response and avoidance of surgery with either therapy.

In those who remain steroid-refractory, approximately 50%–80% respond to IV ciclosporin,^{1,8–11} potentially preventing the need for colectomy. A randomized control trial using 4mg/kg of IV ciclosporin as an induction dose resulted in therapeutic response in 82% of patients, with a mean time of 7 days.¹ One single center, randomized controlled trial demonstrated there was no additional efficacy when dosing ciclosporin at 4 mg/kg IV vs 2 mg/kg, suggesting that using lower dose ciclosporin may improve the toxicity profile while maintaining a beneficial therapeutic response.¹⁸ Whereas lower ciclosporin levels may improve the safety profile of the drug, the optimal target therapeutic range that provides the best efficacy and safety ratio has been a topic of controversy.

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*Department of Medicine, University of Chicago Medical Center, 5841 S Maryland Avenue, Chicago, IL 60637; [†]Department of Gastroenterology, Medical College of Wisconsin, 9200 W. Wisconsin Ave., Milwaukee, WI 53226; [‡]Section of Gastroenterology, Hepatology, and Nutrition, University of Chicago Medical Center, 5841 S Maryland Avenue, MC 4076, Chicago, IL 60637; [§]Division of Gastroenterology, Northwestern University, 676 N. Saint Clair Street, Chicago, IL 60611; [¶]Department of Gastroenterology and Hepatology, Mayo Clinic, 200 1st St SW, Rochester, MN 55902

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*Correspondence address. University of Chicago, 900 East 57th St., MB #9, Chicago, IL 60637. E-mail: jpekow@medicine.bsd.uchicago.edu

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When adequate response to ciclosporin is not achieved, colectomy is often needed.^{19,20} Recent studies suggest that preoperative immunosuppression can adversely affect postsurgical outcomes in inflammatory bowel diseases (IBD).^{21,22} Due to a shorter half-life, ciclosporin may be a safer alternative when compared to infliximab.²³ Nevertheless, whereas drug levels may become undetectable in serum, it is unknown if there is a residual biologic effect impacting the immune system. There also is limited evidence regarding the association between ciclosporin levels, postoperative complications, and drug-related complications.

Thus, whereas it remains highly efficacious in steroid-refractory UC, use of ciclosporin has been limited mainly by lack of familiarity with dosing, potential drug-related and postoperative complications, and a need for close laboratory monitoring. Due to unpredictable pharmacokinetics, utilization of ciclosporin therapy continues to be guided by narrow therapeutic ranges. The primary aim of this study was to evaluate if ciclosporin drug levels are associated with an increased risk of colectomy within 90 days of hospitalization for IV ciclosporin use. Secondary aims were to determine (1) if ciclosporin levels are associated with avoidance of colectomy at 7 and 30 days, (2) if ciclosporin levels are associated with drug-related and postoperative complications, and (3) if additional patient-specific factors are associated with a response to ciclosporin in hospitalized patients with severe UC.

MATERIALS AND METHODS

Patient Population

This study was approved by the University of Chicago Institutional Review Board (IRB# 15-0315). Subjects were identified retrospectively by ICD-9 codes if they had an inpatient admission, a diagnosis of UC, and received ciclosporin as a part of their treatment between May 2008 and June 2015. Electronic medical records were subsequently reviewed for eligibility. Following chart review, patients were included in the analysis only if they had a confirmed diagnosis of UC based on review of all histology and endoscopy reports. Additionally, inclusion criteria included a clinical diagnosis of UC by the treating physician, confirmation that patients received IV ciclosporin after failing treatment with IV corticosteroids, and validation that patient had at least 1 outpatient follow-up encounter after hospital discharge 3 or more months after starting IV ciclosporin. Patients were excluded if they had a diagnosis of Crohn's disease (CD), a history of organ transplantation, lacked at least 1 follow-up encounter, or received ciclosporin before their admission.

The standard management of patients on IV ciclosporin at the University of Chicago is for patients to have their first ciclosporin level checked approximately 48 hours after initiation of therapy and then typically every 24–48 hours during IV therapy. The majority of patients were started on ciclosporin

at 2 mg/kg with dose adjustments to achieve a targeted level of 300 ng/mL–400 ng/mL. Patients who respond to IV ciclosporin are routinely transitioned to oral ciclosporin at an initial dose of twice the final IV dose. This is typically given every 12 hours and patients are concomitantly started on a maintenance therapy with a thiopurine and/or vedolizumab.

Data Collection

Baseline demographic data extracted from medical records at the time of ciclosporin initiation included age, duration of disease, smoking status, prior therapies, gender, and smoking status. Extent of disease was collected from pathology records from previous colonoscopies. In addition, the duration of ciclosporin therapy and levels of ciclosporin throughout the hospitalization were recorded. The University of Chicago laboratory uses liquid chromatography mass spectrometry to measure ciclosporin levels. Prior medications [including use of anti-tumor necrosis factor (anti-TNF) and thiopurines at any time before administration of IV ciclosporin] also were recorded.

Data also were collected on baseline creatinine, potassium levels, hemoglobin, white blood cell count, platelet count, C-reactive protein (CRP), and albumin. Presence of clostridium difficile infection or cytomegalovirus infection at any time before administration of IV ciclosporin also was recorded. Pathology reports also were reviewed and presence of deep ulcers and pancolitis were recorded.

The primary outcome was defined as avoidance of surgical colectomy within 90 days of hospitalization and IV ciclosporin use. Secondary outcomes included avoidance of colectomy at 7 and 30 days, drug-related complications, and postoperative complications. Drug-related complications including infection, tremor, hyperkalemia, headache, and kidney injury (defined as >30% increase in creatinine) also were evaluated. If surgery was performed, date of operation, time from last ciclosporin dose to surgery, and postoperative complications (pelvic infections, surgical wound infections, sepsis, and thrombosis) were extracted from the medical records.

Statistical Analysis

Descriptive statistics were used to examine the baseline characteristics of the cohorts. Continuous variables were compared using Student's *t* test or the Mann-Whitney *U* test (for nonnormally distributed variables). All statistical analysis was performed using JMP 10 software. Normality of continuous variables was evaluated using the Shapiro-Wilk-W test. The chi-square test was used to evaluate distributions of categorical variables, Pearson's correlation (for parametric variables), and Spearman's rank correlation (for nonnormally distributed variables) coefficients were used to evaluate the relationship between continuous variables. Two-sided probabilities were considered, and α values of < 0.05 were considered statistically significant.

RESULTS

Baseline Demographics

A total of 81 patients with severe UC started on IV ciclosporin were included in the analysis. The mean age of the cohort was 33.5 (SD:11) years, 38% (n = 31) of subjects were female, and 14% (n = 11) were active smokers. Over half of the cohort (n = 62, 77%) had pancolonic involvement. The median duration of disease at the start of IV ciclosporin use was 2 years (IQR 1–5). 67% (n = 54) of patients were on thiopurines prior to administration of IV ciclosporin and 16% (n = 13) were previously treated with anti-TNF medications (Table 1). Of these patients, 53% (n = 7) received anti-TNF within 30 days of initiation of ciclosporin.

Clinical Factors Associated With Response (Avoidance of Colectomy) at 7 Days After Initiation of Ciclosporin

21% of the patients (n = 17) required colectomy (nonresponders) within 7 days of starting ciclosporin. There were no differences in the age, sex, disease extent, disease duration, baseline CRP, or albumin levels between patients who responded by day 7 and those without a response to therapy (Supplementary Table 1).

However, responders within 7 days had a higher prevalence of kidney injury while on ciclosporin (39.1% vs 0%, $P = 0.002$), a greater likelihood of previous anti-TNF agent exposure (20.3% vs 0%, $P = 0.03$), and lower rates of cytomegalovirus before receiving IV ciclosporin (1.5% vs 17.6%, $P = 0.007$) when compared to nonresponders (Supplementary Table 1).

Clinical Factors Associated With Response (Avoidance of Colectomy) at 30 Days After Initiation of Ciclosporin

In evaluating response and avoidance of colectomy at day 30, 41% (n = 33) of patients in the cohort required colectomy and were defined as nonresponders. Responders had lower baseline CRP levels (23.6 mg/dL vs 39.7 mg/dL, $P = 0.04$) and fewer deep colonic ulcers by endoscopic evaluation (22.9% vs 42.4%, $P = 0.049$). Patients who had a response at 30 days after starting IV ciclosporin administration also had higher rates of kidney injury (45.8% vs 9.1%, $P = 0.0002$) and prior anti-TNF use (27.1% vs 0%, $P = 0.001$). In addition, patients who failed therapy and underwent a colectomy within the first 30 days after starting ciclosporin were more likely to have pancolitis compared to responders (96.9% vs 62.5%, $P = 0.01$) (Supplementary Table 2).

TABLE 1: Differences between Responders and Non-Responders at 90 days

Variable	All Patients (n,%) n = 81	NonResponders (n,%) n = 47 (58%)	Responders (n,%) n = 34 (42%)	P value
Age [mean in years (SD)]	33.5 (11)	32 (12)	35 (10)	0.29
Female gender [n (%)]	31 (38)	16 (34)	15 (44)	0.36
First Ciclosporin level [median in ng/mL (IQR)]	264 (149)	129.18 (149)	264 (178)	0.9
Mean Ciclosporin level [median in ng/mL (IQR)]	278 (117)	278 (112)	278 (133)	0.94
Peak Ciclosporin level [median in ng/mL (IQR)]	418 (141)	430 (143)	403 (165)	0.83
CRP [mean in mg/L (SD)]	30 (33)	38 (37)	20 (29)	0.01*
White blood cell count [mean in mcL (SD)]	9633 (4135)	7135 (4786)	8920 (3690)	0.32
Platelet count [mean in 10 ³ /mL (SD)]	318 (114)	315 (129)	323 (91)	0.75
Albumin level [mean in g/dL (SD)]	3.6 (0.8)	3.7 (0.7)	3.4 (0.8)	0.03*
Active smoker [n (%)]	11 (14)	5 (10.6)	6 (17.6)	0.37
Deep colonic ulcers [n (%)]	25 (31)	16 (34)	9 (26.5)	0.43
Kidney injury [n (%)]	25 (31)	8 (17)	17 (50)	0.002*
Prior _a Anti-tumor necrosis factor agent use (Anti-TNF) [n (%)]	13 (16)	2 (4.3)	11 (32.4)	<0.0001*
Prior _a immunomodulators use [n (%)]	54 (67)	33 (70.2)	21 (61.8)	0.43
Prior _a Clostridium difficile infection [n (%)]	9 (11)	4 (8.5)	5 (14.7)	0.39
Prior _a Cytomegalovirus (CMV) infection [n (%)]	4 (5)	3 (6.4)	1 (2.9)	0.47
Pancolitis [n (%)]	62 (77)	44 (93.6)	18 (52.9)	.0001*
Disease Duration [mean, years (SD)]	4.49 (6.34)	4.25 (6.32)	4.29 (4.98)	0.97

^a "Prior" refers to use of anti-TNF agents, immunomodulators, or infection with clostridium difficile or CMV at any time point before IV ciclosporin administration.

Clinical Factors Associated With Response (Avoidance of Colectomy) at 90 Days After Initiation of Ciclosporin

58% percent of patients ($n = 47$) required colectomy within 90 days of starting ciclosporin. There were no significant differences in age, gender, duration of disease, or prior use of thiopurines in patients who failed therapy and required surgery within 90 days compared to those who responded to ciclosporin (Table 1). Nonresponders had significantly higher CRP levels (38 mg/dL vs 20 mg/dL, $P = 0.01$), greater albumin levels (3.7 ± 0.7 g/dL vs 3.4 ± 0.8 g/dL, $P = 0.03$) at treatment initiation, and were more likely to have pancolitis (93.6% vs 52.9%, $P = 0.0001$) (Table 1). Responders to IV ciclosporin at 90 days had higher rates of kidney injury (50% vs 17%, $P = 0.002$) and were more likely to have used anti-TNF agents in the past (32.4% vs 4.3%, $P < 0.001$) (Table 1). Similarly, in a subgroup analysis of responders at day 7, pancolitis ($P < 0.001$), higher CRP ($P = 0.02$), higher albumin ($P = 0.02$), and previous anti-TNF use ($P = 0.03$) were associated with colectomy at 90 days and kidney injury trended towards significance ($P = 0.07$). In a separate examination between subjects who previously used anti-TNF therapy and those who never used these agents, there were no differences in baseline variables, except for acute kidney injury on ciclosporin between the 2 groups (Supplementary Table 3).

Both CRP levels ≥ 12 mg/L (OR 2.76 95%CI 1.1–6.96, $P = 0.03$) and albumin ≥ 3.64 g/dL (OR 3.0 95%CI 1.19–7.7, $P = 0.02$) were associated with an increased rate of colectomy at 90 days in a univariate analysis. In contrast, previous treatment with anti-TNF agents was associated with a decreased risk of colectomy at 90 days (OR 0.09 95%CI 0.02–0.46, $P = 0.0005$). After adjusting for the above factors in a multivariate analysis, an albumin level ≥ 3.64 g/dL (OR 3.24, 95%CI 1.02–10.27, $P = 0.04$) and CRP ≥ 12 mg/L (OR 3.58 95%CI 1.14–11.26, $P = 0.03$) remained associated with increased risk of colectomy. Presence of kidney injury was associated with decreased risk of colectomy (OR 0.20, 95%CI 0.06–0.68, $P = 0.001$), however, prior use of anti-TNF agents was not significantly associated with risk of colectomy (OR 0.20, 95%CI 0.03–1.17, $P = 0.07$) (Table 2).

Ciclosporin Levels and Risk of Colectomy at 7, 30, and 90 Days

Initial, mean, and peak ciclosporin levels during IV induction therapy were not significantly different for responders and nonresponders at 7 or 30 days (Supplementary Table 1, 2). Additionally, there was no difference between initial, mean, and peak IV ciclosporin levels among responders and nonresponders at 90 days (Fig. 1). Furthermore, when compared to the lowest quartile of ciclosporin levels, there was not an association with risk of colectomy.

TABLE 2: Multivariate Analysis of Risk Factors Associated with Colectomy within 90 Days of Initiating IV Ciclosporin

Risk factors	Colectomy		
	Odds Ratio	95% Confidence Interval	P value
Kidney Injury	0.20	0.06–0.68	0.01*
^a Prior treatment with anti-tumor necrosis agents	0.20	0.03–1.17	0.07
Albumin on admission ≥ 3.64 g/dL	3.24	1.02–10.27	0.04*
CRP level on admission ≥ 12	3.58	1.14–11.26	0.03*

^a“Prior” refers to use of anti-TNF agents, immunomodulators, or infection with *Clostridium difficile* or CMV at any time point before IV ciclosporin administration.

Ciclosporin Levels and Risk of Postoperative Complications

Of the 47 patients who underwent surgery, 10 patients (21%) had postoperative complications. There were 8 infectious complications (6 wound infections, 1 pelvic infection, and 1 case of sepsis) and 2 noninfectious (1 case of

FIGURE 1. Comparison of responders to ciclosporin with nonresponders within 90 days of hospitalization by first ciclosporin level, mean ciclosporin level, and peak ciclosporin level. Responders defined as those who did not require colectomy, and nonresponders defined as those who underwent colectomy within 90 days of hospitalization. White represents responders and gray represents nonresponders. Bar lines represent total range of levels. Upper and lower box lines represent 75th and 25th percentile, respectively. Line within boxes represents median level.

TABLE 3: Risk of Colectomy at 90 days and Postoperative Complications by Inter-quartile Ciclosporin Levels

Ciclosporin Level (ng/mL)		Colectomy			Complications*		
		Odds Ratio	95% Confidence Interval	P value	Odds Ratio	95% Confidence Interval	P value
1 st Quartile	First (<177)	Ref.			Ref.		
	Mean (<237)	Ref.			Ref.		
	Peak (<347)	Ref.			Ref.		
2 nd Quartile	First (177–263)	1.2	0.43–3.30	0.75	0.64	0.14–3.07	0.59
	Mean (237–277)	1.3	0.46–3.65	0.62	0.3	0.06–1.4	0.13
	Peak (347–418)	1.3	0.46–3.65	0.62	0.3	0.06–1.4	0.13
3 rd Quartile	First (264–330)	1.04	0.43–2.53	0.9	0.95	0.23–3.83	0.94
	Mean (278–354)	0.89	0.37–2.16	0.8	0.6	0.14–2.48	0.47
	Peak (419–490)	1.5	0.62–3.68	0.37	0.48	0.11–2.0	0.3
4 th Quartile	First (>331)	0.95	0.35–2.6	0.92	1.33	0.28–6.26	0.72
	Mean (>355)	0.75	0.28–2.05	0.58	2.78	0.61–12.5	0.19
	Peak (>490)	0.87	0.32–2.4	0.79	0.75	0.13–4.2	0.75

Postoperative complications analyzed in this study include: infections (pelvic infection, surgical wound infections, and presence of sepsis) and noninfectious complications (presence of thrombosis and rehospitalization).

thrombosis, 1 rehospitalization complications). There was not an association between initial, mean, or peak ciclosporin levels and postoperative complications (Table 3). Patients with postoperative complications were more likely, however, to be smokers (40% vs 2.7%, $P = 0.002$) and have higher rates of previous cytomegalovirus infection (30% vs 0%, $P = 0.002$). No other clinical factors were identified to be significantly associated with postoperative complications (Table 4).

In patients who did not respond to ciclosporin and required a colectomy, the average number of days on IV

steroids before initiation of ciclosporin was not different in those who developed postoperative complications compared to those without complications (4.59 days vs 4.25 days, $P = 0.70$). The median discontinuation date of IV ciclosporin before surgery was 5 days. The mean number of days between ciclosporin discontinuation and surgery was greater, although not significantly different in patients without postoperative complications compared to those with postoperative complications (5 days, interquartile range [IQR 1.8–31.3] vs 28 days, [IQR 3.5–135], $P = 0.11$).

TABLE 4: Association Between Clinical Factors and Postoperative Complications

Variable	No Complication n(%) n = 37 (79%)	Complication (n,%) n = 10 (21%)	P value
Age [mean in years (SD)]	32 (12)	33 (13)	0.79
Female gender [n (%)]	12 (32.4)	4 (40)	0.66
CRP [mean in mg/dL (SD)]	34.7 (30)	49 (54)	0.44
Albumin level [mean (SD)]	3.8 (0.7)	3.7 (0.7)	0.75
Active smoker [n (%)]	1 (2.7)	4 (40)	0.002*
Deep colonic ulcers [n (%)]	14 (37.8)	2 (20)	0.27
Kidney injury [n (%)]	8 (21.6)	0	0.11
^a Prior anti-tumor necrosis factor agent use (Anti-TNF) [n (%)]	2 (5.4)	0	0.45
^a Prior use of immunomodulators [n (%)]	27 (73)	6 (60)	0.43
^a Prior clostridium difficile infection [n (%)]	3 (8.1)	1 (10)	0.85
^a Prior cytomegalovirus (CMV) infection [n (%)]	None	3 (30)	0.002*
Days on intravenous steroids before initiation of cyclosporine [mean in days, SD]	4.59 (2.35)	4.25 (2.49)	0.70

^a "Prior" refers to use of anti-TNF agents, immunomodulators, or infection with clostridium difficile or CMV at any time point before IV cyclosporin administration

TABLE 5: Association between Cyclosporin Drug-Associated Complications and Cyclosporin levels

Cyclosporin Level (ng/mL)	Infection (n,%) n = 10 (12.3%)			Tremor (n,%) n = 4 (5%)			Headache (n,%) n = 10 (12.3%)			Hyperkalemia (n,%) n = 3 (4%)			Acute Kidney Injury (Creatinine increase >30%) (n,%) n = 25 (31%)		
	No (n)	Yes (n)	Pvalue	No (n)	Yes (n)	Pvalue	No (n)	Yes (n)	Pvalue	No (n)	Yes (n)	Pvalue	No (n)	Yes (n)	P-value
1 st Quartile															
First (<177)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Mean (<237)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Peak (<347)	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2 nd Quartile															
First (177–263)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mean (237–277)	51	5	0.02*	58	3	0.98	54	7	0.68	57	2	0.75	40	17	0.75
Peak (347–418)	50	7	0.35	59	3	0.94	53	9	0.28	57	3	0.32	40	18	0.38
3 rd Quartile															
First (264–330)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mean (278–354)	34	4	0.33	38	3	0.32	35	6	0.53	39	1	0.54	28	10	0.17
Peak (419–490)	33	5	0.74	39	2	0.98	35	6	0.53	38	2	0.57	27	11	0.38
4 th Quartile															
First (>331)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mean (>355)	15	3	0.76	20	0	0.24	19	1	0.25	19	0	0.32	14	4	0.24
Peak (>490)	14	3	0.67	20	0	0.24	17	3	0.68	19	0	0.32	11	6	0.88

Cyclosporin Levels and Risk of Drug-related Complications

Of the 81 patients treated with IV cyclosporin, 12.3% (n = 10) had an infection, 5% (n = 4) had tremors, 12.3% (n = 10) had headaches, 4% (n = 3) had hyperkalemia, 31% (n = 25) experienced more than a 30% increase in creatinine, and no patients experienced seizures. However, cyclosporin levels were not significantly associated with type or prevalence of complications, including a change in renal function (Table 5).

DISCUSSION

Although several studies have reported a beneficial effect of cyclosporin on the treatment of severe, refractory UC,^{1, 6, 8–11, 16} the optimal cyclosporin range needed to achieve an induction response while minimizing toxicity is not known. One study used a dose of 4 mg/kg/day of cyclosporin in UC patients with an acute flare, with a stable trough ranging between 300 ng/mL and 400 ng/mL.²⁴ However, two analyses have demonstrated that a dose of 2 mg/kg/day with a goal trough ranging between 150 ng/mL and 250 ng/mL or 100 ng/mL and 300 ng/mL appears to have a similar efficacy and may have fewer side effects.^{18, 25} In this cohort of 81 patients treated with IV cyclosporin for induction therapy in severe corticosteroid refractory UC, there was no association between cyclosporin levels and response to therapy at 7, 30, or 90 days, drug-related complications, or postoperative complications. To our knowledge this is the first study to examine the impact of variations in cyclosporin levels irrespective of dose on response and complications in patients with UC.

Although there are limited data examining the impact of variations in cyclosporin levels throughout the treatment course, a previous randomized controlled trial compared 2 mg/kg to 4mg/kg of IV cyclosporin in 73 patients and concluded there was no difference in short-term or long-term colectomy rates.¹⁸ In that study, those receiving the higher treatment dose did have statistically significant higher mean cyclosporin levels (332 ng/mL vs 237 ng/mL), although there were no differences between the treatment groups by day 8. Similarly, a previous analysis from the University of Chicago demonstrated that patients who required colectomy had similar cyclosporin levels during IV induction therapy.⁹ We were able to further substantiate this conclusion in a larger independent cohort by examining the response across greater variations in cyclosporin levels.

The second major conclusion of this study is the identification of patient-specific factors that portend to a greater response rate to cyclosporin induction therapy. We demonstrated that presence of kidney injury, lower serum albumin levels, and lower CRP levels were associated with an increased likelihood of response to cyclosporin and avoidance of colectomy. Kidney injury was defined as greater than 30% increase in creatinine, which is consistent with definitions of injury in previous studies.^{25, 26} Although we used a common definition for acute kidney injury, it varies from other trials that examined renal injury in patients with UC on cyclosporin. For example, in a randomized

controlled trial by D'Haens et al, when using urinary inulin clearance as a measure of renal function, no significant difference was noted in kidney injury rates in those who received cyclosporin.⁷ Although we did not identify an association between cyclosporin level and kidney injury, the development of kidney injury is a known side effect of cyclosporin and could be a marker of its biologic activity independent of the serum drug level.

As opposed to previous observations in patients with severe colitis treated with biologic agents, lower serum albumin levels in this study were associated with an increased likelihood of response to IV cyclosporin.^{27–29} This finding presumably is related to the pharmacodynamics of cyclosporin as it predominantly binds to lipoproteins rather than albumin. In contrast, higher baseline albumin concentrations are associated with increased serum concentrations, lower clearance, and longer half-life of infliximab when compared to those patients with lower serum albumin concentrations.²⁷ Thus, cyclosporin could be considered as a first line salvage therapy over anti-TNF agents in patients with lower serum albumin concentration.

There are several limitations to our analyses. Given the small number of patients with a mean level below 200 ng/mL, this analysis was limited in assessing response and safety in a population with targeted dosing of low levels of cyclosporin. As such, these findings may not be generalizable to other medical centers where strategies to target lower serum levels are utilized. In addition, we were unable to evaluate levels in patients after transition to oral cyclosporin given variation in frequency of obtaining levels and timing of levels in relation to an individual's last dose of cyclosporin. This limited our ability to assess for other confounding factors that may have resulted in a delayed decrease in response to therapy such as noncompliance, cessation of medication due to side effects, and failure to maintain remission when transitioned to a thiopurine or vedolizumab. A previous analysis from our group examining an independent cohort, however, did demonstrate that patients who eventually underwent colectomy while on oral cyclosporin had lower levels than patients who avoided surgery.⁹ Furthermore, due to the nature of this retrospective study, there was absence of randomization, variation of induction dosing, individual provider management, and varied follow-up intervals. In addition, different methods of measuring cyclosporin levels, such as cyclosporin clearance, may provide additional information and benefit. All of these factors have the potential to alter the 7, 30, or 90-day colectomy risk.

In summary, clinical response as well as nonsurgical and postoperative complications were not associated with the initial, mean, or peak serum cyclosporin levels during IV induction therapy. Although we were not able to examine the impact of dose escalation on response in this study, we did not observe an association between clinical response to cyclosporin treatment and therapeutic drug range during IV induction therapy. Instead, CRP levels and presence of kidney injury may be more helpful in predicting a clinical response to cyclosporin in patients with severe UC.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

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