Scandinavian Journal of Gastroenterology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/igas20

Long-term outcomes of patients with acute severe ulcerative colitis treated with cyclosporine rescue therapy

Heli Eronen, Pia Oksanen, Airi Jussila, Heini Huhtala, Ilona Helavirta & Tuire Ilus

To cite this article: Heli Eronen, Pia Oksanen, Airi Jussila, Heini Huhtala, Ilona Helavirta & Tuire Ilus (2022): Long-term outcomes of patients with acute severe ulcerative colitis treated with cyclosporine rescue therapy, Scandinavian Journal of Gastroenterology, DOI: 10.1080/00365521.2022.2143727

To link to this article: https://doi.org/10.1080/00365521.2022.2143727

Published online: 17 Nov 2022.

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY
https://doi.org/10.1080/00365521.2022.2143727

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Long-term outcomes of patients with acute severe ulcerative colitis treated with cyclosporine rescue therapy

Heli Eronen[a,b], Pia Oksanen[b,c], Airi Jussila[c], Heini Huhtala[d], Ilona Helavirta[c] and Tuire Ilus[c]

[a]Department of Gastroenterology, Kanta-Häme Central Hospital, Hämeenlinna, Finland; [b]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [c]Department of Gastroenterology and Alimentary Tract Surgery, Tampere University Hospital, Tampere, Finland; [d]Faculty of Social Sciences, Tampere University, Tampere, Finland

ABSTRACT

Background and aims: The early outcomes of ulcerative colitis (UC) after rescue therapy with cyclosporine A (CyA) are well known. Published data on the safety of this treatment in perioperative use and data on the long-term prognosis are scarce and are investigated here.

Methods: All UC patients treated with CyA in Tampere University Hospital between 2009 and 2018 were reviewed from patient records.

Results: A total of 182 patients were included with the median follow-up of 3.8 (range 0-13) years. Of all patients, 139 (76%) responded to CyA. A quarter of the responders achieved long-term remission and used thiopurines as maintenance therapy at the end of follow-up. Altogether 83 (46%) needed further enhancement of treatment with corticosteroids (Cs) and 57 (31%) with biologicals or small molecules. Of the nonresponders 27 (55%) were treated surgically within admission to index flare. Infliximab was used as a third-line rescue therapy for 16 patients of whom four benefitted. The overall colectomy rate in this series was 45%. When compared to Cs alone CyA did not increase the risk for severe postoperative complications in patients treated for severe treatment-refractory UC.

Conclusion: In conclusion, despite the good initial response to CyA, a large proportion of patients relapsed during long-term follow-up and the colectomy rates remain high. Other therapy attempts after failure of CyA merely postpone surgery in many. We therefore recommend informing patients about the possibility of surgery prior to the initiation of rescue therapy.

ARTICLE HISTORY
Received 23 September 2022
Revised 20 October 2022
Accepted 31 October 2022

KEYWORDS
Inflammatory bowel disease; ulcerative colitis; cyclosporine A; rescue therapy; infliximab

Introduction

Ulcerative Colitis (UC) is a chronic inflammatory bowel disease (IBD) following a remitting-relapsing course. Up to 20% of patients experience acute severe UC (ASUC), a life-threatening condition requiring admission to hospital [1]. Although the role of corticosteroids (Cs) in the treatment of acute flare is well established, studies show that up to 30% of patients with ASUC are refractory to Cs [2,3].

The need for surgery among patients with IBD has decreased in recent decades but many patients with ASUC still require surgical treatment [4–7]. High colectomy rates indicate the need for rescue therapies. Cyclosporine A (CyA) and Tacrolimus, calcineurin inhibitors as well as a tumor necrosis alpha inhibitor infliximab (IFX) have emerged as effective options and have been shown to be equally effective in steroid refractory ASUC at least in short-term use [8,9].

CyA induces remission in up to 85% of patients with ASUC but overall colectomy rates still remain high [10–12]. The long-term efficacy of CyA rescue therapy has been a topic of debate and data on the perioperative safety of the treatment in UC patients is scarce and investigated here.

Materials and methods

All patients admitted to Tampere University Hospital for acute flare of UC between January 2009 and December 2018 were identified from the digital patient records. Patients aged 16 years or over and treated with CyA as a rescue therapy for ASUC were included.

Collected data included demographic (gender, age, smoking, and other diseases), clinical (UC duration, extent of the disease, disease severity at index flare, and recurring flares), biological (laboratory results [hemoglobin, leukocytes, c-reactive protein, albumin, fecal calprotectin] at index flare) and treatment data (prior corticosteroid [Cs] usage, need for further Cs therapy, thiopurines, need for biologicals, small molecules, or colectomy in follow-up).

UC was diagnosed on the basis of clinical history, symptoms, endoscopic, and histological features. Disease extent was categorized by the Montreal classification and the severity of the flare was assessed by the Mayo scoring system based on clinical and endoscopic characteristics [13]. ASUC was characterized by more than six bloody stools per day along with any of the following: tachycardia, fever, anemia,

CONTACT Heli Eronen heli.eronen@fimnet.fi Faculty of Medicine and Health Technology, Kanta-Hämeen Sairaanhoitopiirin Kuntayhtymä, Heli Eronen, Ahvenistontie 20, Hameenlinna 13530, Finland

and/or ESR >30 mm/h (Truelove and Witt's criteria) [14]. Comorbidity was defined using the Charlson comorbidity index [15].

CyA was used as a rescue therapy for ASUC and thiopurines as maintenance therapy. CyA was initiated as an intravenous induction at dose of 2 mg/kg/day [16]. Dose adjustments were made according to drug levels measured every 48–72 h targeting therapeutic levels. In patients with clinical response, intravenous CyA was switched to peroral and adjusted to drug levels. After three to seven days of induction, thiopurine was initiated.

Alleviation of UC was defined as clinical response to rescue therapy with no need for colectomy or third-line rescue therapy at index flare. Relapse was defined as requiring further Cs treatment, re-hospitalization, biologicals, small molecules, or colectomy later in follow-up. Patients were followed-up from the date of the index flare until colectomy, death, or the end of the observation period. Adverse events related to CyA were assessed.

Surgical complications were defined using the Clavien-Dindo classification (grades III–V classified as severe complications) [17]. The surgical complications in CyA-treated patients ($N = 32$) were compared to all patients operated on (colectomy with temporary ileostomy) for severe treatment-refractory UC in Tampere University Hospital within the same follow-up period. For purposes of comparison, the procedures in which proctectomy and IPAA (ileal-pouch anal anastomosis) were performed in the same procedure were excluded.

Table 1. Clinical characteristics of the 182 patients with ASUC treated with CyA.

	n/median	%/range
Follow-up time (yr)	3.7	0–13
Male	93	51
Smoker	31	17
Age at diagnosis (yr)	30	9–76
Age at index flare (yr)	32	16–76
Disease duration at index flare (yr)	0.9	0–36
Montreal score		
E1	2	1
E2	52	29
E3	128	70
Endoscopic severity Mayo 3	124	68
CCI	0	0–3

CCI: Charlson comorbidity index; E1: proctitis; E2: left sided colitis; E3: pancolitis.
Data expressed as absolute and relative frequencies and medians.

Statistical analyses

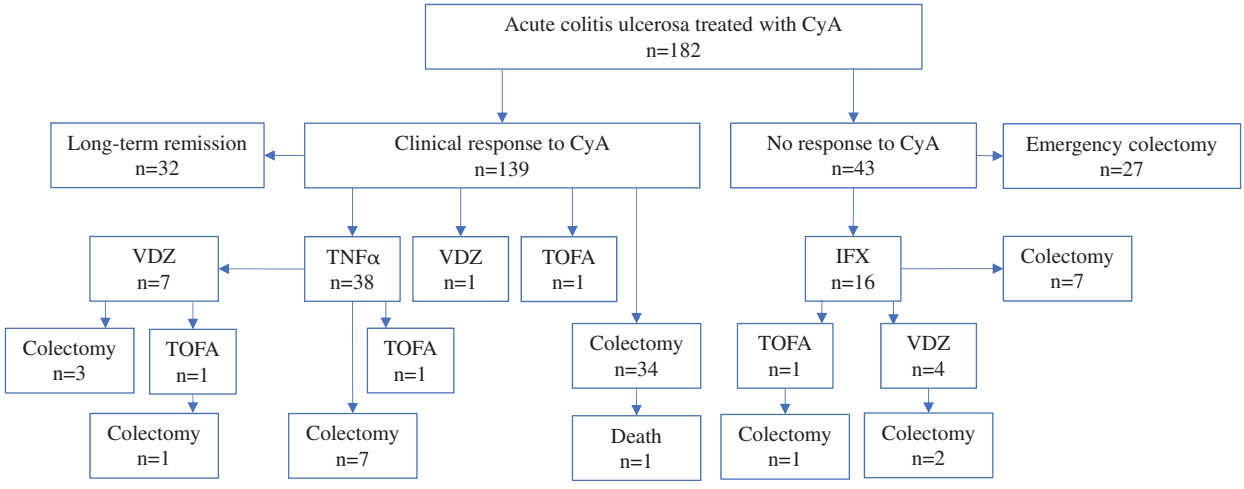
The statistical analyses were conducted with IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp). The data are presented as median with range (minimum–maximum) for numerical variables and number and percentage (%) for categorical variables. The characteristics of those responding to Cyclosporine and nonresponders were compared with chi square or Fisher's exact test. The Kaplan-Meier curve was used to present cumulative colectomy rate. The study was approved by the regional review board (R19617). Due to the retrospective nature of this study, no ethical approval was required.

Results

Baseline characteristics are shown in Table 1. In total, 182 patients were included with median follow-up of 3.8 (0–13) years. The majority of patients (68%) had endoscopically severe disease (defined as Mayo Score 3) with inflammation extending throughout the entire colon (70%).

As shown in Figure 1, 139 (76%) patients responded to treatment. Of the responders 32 (23%) were in long-term remission with no need for further Cs, rehospitalization, or enhancement of therapy with biologicals or small molecules (tofacitinib) during follow-up.

Clinical outcomes of the patients are shown in Table 2. Fifty-two (29%) patients were taking thiopurines alone or in combination with mesalamine as maintenance therapy at the end of follow-up. Of all patients treated with CyA 83 (46%) needed further enhancement of treatment with Cs and 57 (31%) with biologicals or small molecules.



CyA, Cyclosporine A; TNFα, TNF alpha inhibitor, VDZ, vedolizumab; TOFA, tofacitinib; IFX, infliximab.

Figure 1. Clinical outcomes of 182 patients treated with CyA.

Despite the good initial response to CyA 45 (32%) of the responders needed surgery, 13 of whom were operated on after failing one to three different trials with biologicals or small molecules (Figure 1). Of the nonresponders 27 (55%) needed surgery on admission for index flare, 34 (79%) underwent surgery within the first year after treatment and overall, 37 (86%) lost their colons during follow-up (Figure 2). Sixteen patients were treated with IFX as a third-line rescue therapy, of whom 10 (63%) were operated on within 5 months (range 0–45) of follow-up after admission due to index flare. The cumulative colectomy rate of patients treated with CyA is shown in Figure 2. Of all patients 34 (19%) and 65 (36%) were operated on within 1 and 12 months of follow-up, respectively (Table 2). The overall colectomy rate in this series was 82 (45%). The one death reported was neither IBD nor treatment related.

In the same follow-up period (between January 2009 and December 2018), 107 patients were operated on (colectomy with temporary ileostomy) in Tampere University Hospital for severe treatment-refractory UC. Fifty-three of those patients had surgical complications, of which 22 were considered severe (defined as Clavien-Dindo grades III–V). When compared to Cs alone CyA did not increase the risk for severe postoperative complications (Table 3).

Thirty-seven CyA-related adverse events were reported in 30 (16%) patients leading to discontinuation of treatment in 28. There was no difference when comparing adverse events in patients with peroral 2 (15%) and intravenous 28 (17%) administration of CyA. Leukopenia (2%), liver toxicity (2%), paraesthesia (1%), abscess (1%), clostridium difficile infection (1%), and pulmonary reaction (1%) were significant adverse events reported by 14 (8%) patients. Adverse events were mostly reversible, except in two patients nausea did not diminish with discontinuance of treatment. Three patients (2%) had anaphylaxis as SAE.

The prognostic factors of patients responding to CyA and patients failing to respond to treatment are shown in Table 4. Gender, smoking or endoscopic severity at index flare did not predict the clinical outcome. Peroral administration of CyA was a significant predictor for response to rescue therapy whereas the extent of the disease predicted the need for surgery.

Table 2. Clinical outcome of the 182 patients with ASUC treated with CyA.

	n/median	%/(range)
Clinical response to treatment	139	76
Duration of treatment with CyA (d)	90	(1–479)
Thipurine as maintenance therapy after CyA	121	66
Thiopurine as maintenance therapy at the end of follow-up	52	29
Need for Cs within follow-up	83	46
Rehospitalization after index flare	55	30
Need for biologics and small molecules within follow-up	57	31
Colectomy		
Median age for colectomy (y)	32	(18–66)
Median time from diagnosis to colectomy (y)	2	(0–25)
Median time from index flare to colectomy (y)	0	(0–5)
Emergency colectomy	27	15
Colectomy within one month of treatment	34	19
Colectomy within three months of treatment	40	22
Colectomy within one year of treatment	65	36
Overall colectomy within follow-up	82	45

CyA: cyclosporine A; Cs: corticosteroids.
Data expressed as absolute and relative frequencies and medians.

Discussion

In this series three out of four patients responded to rescue therapy with CyA but only a quarter achieved long-term remission and took thiopurines as maintenance therapy at the end of follow-up. One third of the patients with initial response to CyA required enhancement of treatment with biologicals or small molecules and equally as many eventually underwent surgery. Of the patients failing to respond to CyA almost 90% required surgery despite several subsequent treatment attempts.

Earlier studies have reported up to 86% short-term response rates for rescue therapy with CyA [18]. However, the efficacy of the treatment seems to disappear over time, leading to relapse and colectomy rates of up to 90% [10,12]. Studies show that maintenance therapy with thiopurines is required to maintain response to CyA in the long run [18,19].

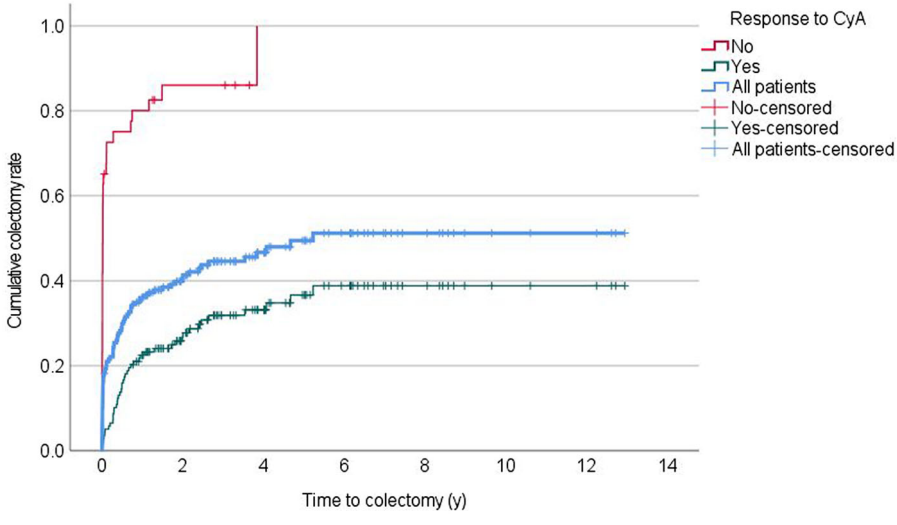


Figure 2. Cumulative colectomy rate in the 182 patients treated with CyA.

Table 3. Surgical complications of the 107 patients operated on for treatment-refractory UC in Tampere University Hospital 2009–2018.

Preoperative medication	Surgical complications *n/N*	%	Severe surgical complications *n/N*	%	Severe surgical complications reported (*n*)
No medication	2/4	50	1/4	25	Septicemia and abscess (1)
Corticosteroid	31/57	54	14*/57	24	Fascia rupture (4), pulmonary embolism (2), abscess (2), massive bleeding (2), wound rupture (2), strangulation (2), pneumonia (1), wound infection (2), stroke (1), pneumothorax (1)
CyA + Cs	15/32	47	5/32	16	Massive bleeding (3), necrotic infection in ileostomy (1), strict ileostomy (1).
Infliximab + Cs	3/11	27	1/11	9	Perforation (1)
Vedolizumab + Cs	1/2	50	1/2	50	Perforation after strangulation (1)
Tofacitinib	1/1	50	0/1	0	

Cs: corticosteroid.
Surgical complications were defined using Clavien-Dindo classification, grades III–V classified as severe.
*In five patients several complications were reported.

Table 4. Prognostic factors for response to CyA in 182 patients.

	Responders		Nonresponders		*p*-value
	n/median	% (range)	*n*/median	% (range)	
Gender					0.720
Male	70	75	23	25	
Female	69	78	20	22	
Smoking					0.230
Smoker	24	77	7	23	
Nonsmoker	87	80	22	20	
Montreal score					0.01
E1	2	100	0	0	
E2	45	87	7	14	
E3	94	73	34	27	
Endoscopic severity					0.821
Mayo 1	2	100	0	0	
Mayo 2	37	79	10	21	
Mayo 3	93	75	31	25	
CyA administration					0.040
Peroral	13	100	0	0	
Intravenous	126	75	43	25	

CyA: cyclosporine A.

However, as seen in our series despite promising initial response to treatment, less than quarter of patients remained asymptomatic with thiopurines during long-term follow-up.

A prior randomized trial (CONSTRUCT) reported no significant difference between rescue therapy with CyA or IFX regarding the effectiveness, safety, and tolerability of these treatments in 3-year follow-up [20,21]. A study by Laharie et al. showed comparable efficacy and good safety profile for both CyA and IFX in 5-year follow-up and did not favor one treatment over another [22]. Since then, IFX has appeared to be superior to CyA in terms of treatment response and lower colectomy rates in long-term follow-up at least in non-randomized studies [9,23].

The use of CyA as a salvage therapy is based on an idea of rapidly induced remission and acting as a bridge therapy for maintenance therapies with slow acting agents such as thiopurines. Thiopurines are widely used for the treatment of IBD but some serious concerns about the safety of the treatment have been raised in recent years [24]. In this series, only one quarter of patients continued thiopurines as maintenance therapy and one third needed enhancement of treatment with biologicals or small molecules. The results would suggest that CyA no longer has a place in the treatment of Cs-refractory ASUC in the era of biologicals. Furthermore, considering reduced costs due to biosimilars, good tolerability and simple monitoring IFX is already preferred as the primary rescue therapy in many centers. However, as seen in a recent study by Atia et al. the widespread use of biologicals has not reduced colectomy rates in UC patients as might have been expected [25].

The term third-line rescue therapy is used for the sequential trial of rescue therapy used for patients with Cs-refractory UC after failed attempts with the first rescue therapy trial with CyA or IFX. In earlier studies, third-line rescue therapy was effective in inducing remission in the short term [4,26]. In this series, a quarter of patients benefited from IFX after failure to respond to CyA. However, for some, any subsequent trials only prolonged the severe condition. Although surgery in UC is likely to reduce symptoms, not all patients are willing to go through invasive treatment. However, as seen in this series, successive trials only prolonged severe condition and in many delayed the inevitable surgery.

Complications related to CyA have mostly been reported to be reversible but SAE and even mortality due to opportunistic infections have been observed [27,28]. In our series, 15% of patients discontinued treatment due to side effects. Our results are in line to those previously reported [18,22]. Although most of the adverse events were reversible, significant complications were reported in 8% and life-threatening anaphylaxis in 2% of patients. Thus, close monitoring of patients treated with CyA is advised.

Earlier studies as well as our series showed no increased risk for surgical complications in patients treated with CyA when compared to Cs alone [29]. However, as is known, delayed surgery is associated with increased risk for postoperative complications in ASUC [30]. The long delay waiting for the response to different therapy trials may explain the high number of post-operative complications. Therefore, it is important to consult a surgeon prior to rescue therapy and discuss with the patient the option of surgical treatment in Cs-refractory ASUC.

The extent of the disease seemed to predict response to treatment in this study. This may be due to the milder disease course of patients with proctitis when compared to patients with severe inflammation in pancolitis. Also, patients

not receiving induction with intravenous CyA were more likely to respond to treatment. This may be explained by the fact that those patients treated with perorally administered CyA alone were likely to have a milder disease course when compared to hospitalized patients treated with intravenous CyA.

This study provides more information on the perioperative safety of CyA in UC patients while published data and official guidelines are limited. The data on the long-term efficacy of CyA in Cs-refractory UC is controversial. Our series provides more information and presents the results of one tertiary center on these topics. The number of patients and the duration of this study are comparable to those reported earlier. The limitations of our study are due to its retrospective nature and to relying on patient records.

In conclusion, despite the reasonably encouraging initial response to CyA, a large proportion of patients relapsed during long-term follow-up. In many of the nonresponders, third-line rescue therapy with IFX only delayed inevitable surgery. We therefore recommend informing patients of the option for surgery prior to initiation of rescue therapy.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

HE reports a personal research grant from the Emil Aaltonen Foundation and speaker's fees from Tillots Pharma. PO reports congress fees from Ferring, Abbvie, Pfizer, and consultancy fees from Tillotts and Gilead. AJ has received speaker's or consultant's fees from Abbvie, Pfizer, and Takeda. HH has nothing to declare. IH reports having received a research grant from the Mary and Georg Ehnrooth Foundation, a congress fee from Takeda, speakers' fees from the Crohn's and Colitis Association and Hollister, consultancy fees from Hotus. TI reports advisory board Janssen, Celltrion, Takeda and speaker's fee Tillotts, Takeda, Janssen.

ORCID

Heini Huhtala http://orcid.org/0000-0003-1372-430X

References

[1] Hindryckx P, Jairath V, D'Haens G. Acute severe ulcerative colitis: from pathophysiology to clinical management. Nat Rev Gastroenterol Hepatol. 2016;13(11):654–664.

[2] Faubion WA Jr, Loftus E. V. Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterol. 2001;121(2):255–260.

[3] Harbord M, Eliakim R, Bettenworth D, European Crohn's and Colitis Organisation [ECCO], et al. Third european evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. J Crohns Colitis. 2017;11(7):769–784.

[4] Feuerstein JD, Akbari M, Tapper EB, et al. Systematic review and meta-analysis of third-line salvage therapy with infliximab or cyclosporine in severe ulcerative colitis. Ann Gastroenterol. 2016; 29(3):341–347.

[5] Eriksson C, Cao Y, Rundquist S, et al. Changes in medical management and colectomy rates: a population-based cohort study on the epidemiology and natural history of ulcerative colitis in Orebro, Sweden, 1963-2010. Aliment Pharmacol Ther. 2017;46(8): 748–757.

[6] Turner D, Walsh CM, Steinhart AH, et al. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol. 2007;5(1): 103–110.

[7] Frolkis AD, Dykeman J, Negrón ME, et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterol. 2013;145(5):996–1006.

[8] Duijvis NW, Ten Hove AS, Ponsioen CIJ, et al. Similar short- and long-term colectomy rates with ciclosporin and infliximab treatment in hospitalised ulcerative colitis patients. J Crohns Colitis. 2016;10(7):821–827.

[9] Narula N, Marshall JK, Colombel J-F, et al. Systematic review and Meta-Analysis: infliximab or cyclosporine as rescue therapy in patients with severe ulcerative colitis refractory to steroids. Am J Gastroenterol. 2016;111(4):477–491.

[10] Campbell S, Travis S, Jewell D. Ciclosporin use in acute ulcerative colitis: a long-term experience. Eur J Gastroenterol Hepatol. 2005; 17(1):79–84.

[11] van Assche G, Vermeire S, Rutgeerts P. Treatment of severe steroid refractory ulcerative colitis. World J Gastroenterol. 2008; 14(36):5508–5511.

[12] Moskovitz DN, Van Assche G, Maenhout B, et al. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. Clin Gastroenterol Hepatol. 2006;4(6):760–765.

[13] Magro F, Gionchetti P, Eliakim R, European Crohn's and Colitis Organisation [ECCO], et al. Third european evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. J Crohns Colitis. 2017;11(6):649–670.

[14] Dignass A, Eliakim R, Magro F, et al. Second european evidence-based consensus on the diagnosis and management of ulcerative colitis part 1: definitions and diagnosis. J Crohns Colitis. 2012; 6(10):965–990.

[15] Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–383.

[16] Van Assche G, D'Haens G, Noman M, et al. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. Gastroenterology. 2003;125(4): 1025–1031.

[17] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205–213.

[18] Cohen RD, Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. Am J Gastroenterol. 1999;94(6): 1587–1592.

[19] Miyake N, Ando T, Ishiguro K, et al. Azathioprine is essential following cyclosporine for patients with steroid-refractory ulcerative colitis. World J Gastroenterol. 2015;21(1):254–261.

[20] Williams JG, Alam MF, Alrubaiy L, et al. Comparison of infliximab and ciclosporin in steroid resistant ulcerative colitis: pragmatic randomised trial and economic evaluation (CONSTRUCT). Health Technol Assess. 2016;20(44):1–320.

[21] Williams JG, Alam MF, Alrubaiy L, et al. Infliximab versus ciclosporin for steroid-resistant acute severe ulcerative colitis (CONSTRUCT): a mixed method, open-label, pragmatic randomised trial. Lancet Gastroenterol Hepatol. 2016;1(1):15–24.

[22] Laharie D, Bourreille A, Branche J, Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open label randomised controlled trial. Lancet. 2012;380(9857):1909–1915.

[23] Thorne K, Alrubaiy L, Akbari A, et al. Colectomy rates in patients with ulcerative colitis following treatment with infliximab or ciclosporin: a systematic literature review. Eur J Gastroenterol Hepatol. 2016;28(4):369–382.

[24] de Boer NKH, Peyrin-Biroulet L, Jharap B, et al. Thiopurines in inflammatory bowel disease: new findings and perspectives. J Crohns Colitis. 2018;12(5):610–620.
[25] Atia O, et al. Colectomy rates did not decrease in paediatric- and Adult-Onset ulcerative colitis during the biologics era: a nationwide study From the epi-IIRN. J. Crohns Colitis. 2021;16(5):796–803.
[26] Chaparro M, Burgueño P, Iglesias E, et al. Infliximab salvage therapy after failure of ciclosporin in corticosteroid-refractory ulcerative colitis: a multicentre study. Aliment Pharmacol Ther. 2012;35(2):275–283.
[27] Arts J, D'Haens G, Zeegers M, et al. Long-term outcome of treatment with intravenous cyclosporin in patients with severe ulcerative colitis. Inflamm Bowel Dis. 2004;10(2):73–78.
[28] Sternthal MB, Murphy SJ, George J, et al. Adverse events associated with the use of cyclosporine in patients with inflammatory bowel disease. Am J Gastroenterol. 2008;103(4):937–943.
[29] Nelson R, Liao C, Fichera A, et al. Rescue therapy with cyclosporine or infliximab is not associated with an increased risk for postoperative complications in patients hospitalized for severe steroid-refractory ulcerative colitis. Inflamm Bowel Dis. 2014;20:14–20.
[30] Randall J, Singh B, Warren BF, et al. Delayed surgery for acute severe colitis is associated with increased risk of postoperative complications. Br J Surg. 2010;97(3):404–409.