Journal of Crohn's and Colitis (2014) **8**, 1427–1437

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ScienceDirect

The effectiveness and safety of rescue treatments in 108 patients with steroid-refractory ulcerative colitis with sequential rescue therapies in a subgroup of patients

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Received 30 March 2014; received in revised form 11 May 2014; accepted 18 May 2014

KEYWORDS
Ulcerative colitis;
Tacrolimus;
Ciclosporin;

Abstract

Background: Among patients with steroid-refractory ulcerative colitis (UC) in whom a first rescue therapy has failed, a second line salvage treatment can be considered to avoid colectomy.

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http://dx.doi.org/10.1016/j.crohns.2014.05.004

Infliximab;
Inflammatory bowel disease

Aim: To evaluate the efficacy and safety of second or third line rescue therapy over a one-year period.
Methods: Response to single or sequential rescue treatments with infliximab (5 mg/kg intravenously (iv) at week 0, 2, 6 and then every 8 weeks), ciclosporin (iv 2 mg/kg/daily and then oral 5 mg/kg/daily) or tacrolimus (0.05 mg/kg divided in 2 doses) in steroid-refractory moderate to severe UC patients from 7 Swiss and 1 Serbian tertiary IBD centers was retrospectively studied. The primary endpoint was the one year colectomy rate.
Results: 60% of patients responded to the first rescue therapy, 10% went to colectomy and 30% non-responders were switched to a 2nd line rescue treatment. 66% of patients responded to the 2nd line treatment whereas 34% failed, of which 15% went to colectomy and 19% received a 3rd line rescue treatment. Among those, 50% patients went to colectomy. Overall colectomy rate of the whole cohort was 18%. Steroid-free remission rate was 39%. The adverse event rates were 33%, 37.5% and 30% for the first, second and third line treatment respectively.
Conclusion: Our data show that medical intervention even with 2nd and 3rd rescue treatments decreased colectomy frequency within one year of follow up. A longer follow-up will be necessary to investigate whether sequential therapy will only postpone colectomy and what percentage of patients will remain in long-term remission.

1. Introduction

Ulcerative colitis (UC) is a lifelong disease arising from an interaction between genetic and environmental risk factors. Mild or moderate disease is effectively treated with systemic and/or topical 5-ASA preparations.[1] Steroids are still the main stay of therapy for the induction of remission in severe forms of UC. However, almost 40% of patients with a severe flare of UC do not respond sufficiently to systemic steroids.[2,3] Calcineurin inhibitors, such as ciclosporin and tacrolimus (Tcl) as well as anti-TNF-antibodies, such as infliximab (IFX) (or adalimumab and golimumab as evident from recent clinical studies) are current therapeutic options in steroid-refractory UC. The optimal choice remains controversial despite the results of a randomized study of ciclosporin versus IFX in severe UC failing to respond to steroids.[4] Short term response rates with avoidance of colectomy reached 85% for both drugs without significant difference. Data from randomized trials and clinical experience regarding Tcl in steroid refractory UC are limited so far.[5,6]

Among patients with steroid-refractory UC in whom first rescue therapy has failed, a second line salvage treatment can be considered to avoid colectomy. Although this approach may be beneficial, sequential use of rescue treatments is potentially risky because of the cumulative immunosuppressive effects.[7] This is especially important when IFX is given as the first line therapy. Serum levels of IFX typically remain increased for at least 8 weeks.[8] Therefore, if ciclosporin (or Tcl) is initiated in IFX resistant cases, within less than 8 weeks after the last infusion, the risk for infectious complications may increase.

There are only limited data concerning the efficacy of second line rescue treatment in case of failure of the first line therapy. Maser et al. published a small retrospective study presenting the efficacy rates of IFX after ciclosporin failure and ciclosporin after IFX failure. These treatment options reached 40% and 33% respectively.[9] Chaparro and colleagues [7] showed that second line treatment with IFX was effective in avoiding colectomy in the short term in two thirds of patients with steroid-refractory UC in whom ciclosporin failed. Still, the authors emphasized the association with a high rate of adverse events and even mortality. The GETAID group reported in 2011 the largest series of patients treated with a second line salvage therapy[10] with one year colectomy free survival of 41%.

Both, the European Crohn's and Colitis Organization (ECCO) and the American College of Gastroenterology (ACG) recommend the use of a second line rescue therapy only in expert centers and colectomy after failure of a second-line therapy with either ciclosporin or IFX.[2,11]

Our goal was to assess the effectiveness and safety of a second or third line rescue therapy in a cohort of 108 corticosteroid refractory patients.

2. Methods

2.1. Patients

108 patients with steroid refractory UC from 7 Swiss (91 patients) and 1 Serbian centers (17 patients) were enrolled in the cohort. Patients with confirmed UC diagnosis treated with Tcl, ciclosporin or IFX were identified from the Swiss national inflammatory bowel disease (IBD) cohort database and the IBD register of the Department of Gastroenterology in University Hospital "Zvezdara", Belgrade, Serbia. MP (IBD specialist from University Hospital Zvezdara, Belgrade, Serbia) currently works in Switzerland. Therefore we had the opportunity to obtain and integrate the data from the Serbian center, which follows exactly the same therapeutic strategy for IBD treatment like the other Swiss tertiary centers.

In all patients, disease diagnosis had been achieved according to standard clinical, endoscopic, radiologic and histologic criteria.[12] Disease location was categorized according to the Montreal classification[13] (ulcerative proctitis, left-sided and extensive colitis). Steroid resistance was defined as a lack of

Table 1 Baseline patient's characteristics treated with first, second or third rescue treatment in steroid refractory UC.

	Only 1 rescue Treatment	2 rescue Treatments	All 3 rescue Treatments
Number of patients	76	26	6
Gender (female) %	38.2	38.5	33.3
Age (y)	39.5 (16–90)	37.0 (18–60)	41.5 (19–55)
Disease duration (y)	5.0 (0–35)	4.0 (0–22)	3.5 (1–6)
Disease location: (%)			
Extensive colitis	64.5	57.7	66.7
Left sided colitis	35.5	42.3	33.3
MTWSI score at induction date (M ± IQR)	13 ± 4	13 ± 5	14 ± 7
CRP at induction date (mg/L) (M ± IQR)	20 ± 48	18 ± 34	17 ± 66
Severity of disease (MTWSI):			
Severe disease	60.5	69.2	66.7
Moderate disease	39.5	30.8	33.3
Reasons for 2nd/3rd salvage th:			
Primary rescue failure	/	42.3	33.3
Loss of response	/	46.2	50.0
Intolerance/side effects (%)	/	11.5	16.7
Concom. IMD therapy (%)	31.6	26.9	16.7
Previous IMD therapy failure (%)*	79	88	84
Dose of CS at induction date (M ± IQR) (mg)	40 ± 20	45 ± 20	50 ± 20
Length of CS (M ± IQR) therapy (d)	56 ± 56	63 ± 43.75	42 ± 47.75

Failure* implies resistance, intolerance and insufficient response.
Abbreviations: M, median; IQR, interquartile range; CRP, C-reactive protein; IMD, immunomodulators; CS, corticosteroids; d, days.

response to a systemic daily dose of prednisolone of 0.75 mg/kg over a period of 4 weeks.[12] The inclusion criteria allowed us to enroll patients who failed either the oral steroid treatment (see above) or to a high-dose intravenous steroid therapy (with methylprednisolone 60–125 mg/24 h or equivalent hydrocortisone 100 mg 4 times daily for 7–10 days). The steroid reduction and weaning were agreed by the protocol of the study. The median dose of corticosteroids at the beginning of the rescue treatment and median length of corticosteroid therapy are shown in Table 1.

The medical records of all these patients were reviewed in the period from 2010 to 2013. We evaluated patients with either a

1. Single rescue treatment with IFX or ciclosporin or Tcl or
2. Sequential treatments with IFX and calcineurin inhibitors (CI – ciclosporin, Tcl) and vice versa [with a delay of >3 days <1 month between CI (when used first) and IFX, and a delay of >6 weeks <2 months between IFX (when used first) and CI. The interruption period between ciclosporin and Tcl (and vice versa) was >3 days <1 month].

The time intervals between therapies were defined according to a protocol. Eight patients were excluded from analysis due to longer interruption period between two rescue therapies. The colectomy was recommended when patients presented with severe or fulminant disease either as a result of primary non-response or loss of response to the rescue therapy. The evaluation of therapeutic response during a severe attack (or relapse) was made according to the Oxford criteria (stool frequency >8 and CRP >45 mg/L on day 3)[14] and radiology (toxic mega colon). All decisions were made among patients, gastroenterologist and surgeon. According to the ECCO guidelines[2] the same indications for colectomy are being applied in all Swiss and Serbian tertiary centers.

2.2. Medications

For the patients treated with IFX, regardless whether used as a first, second or third line therapy, an induction therapy week 0, 2 and 6 was planned (dose ≥5 mg/kg). Responders received a maintenance therapy (5 mg/kg intravenously). Ciclosporin was started intravenously at an initial dose of 2 mg/kg/day up to 4 mg/kg/day for at least 2 days (aiming for serum trough levels of 150–200 ng/mL). In case of response, after 7 days, ciclosporin was switched to oral preparations (5 mg/kg/daily) for at least 3 months. After a successful initial rescue treatment with ciclosporin, standard maintenance therapy with thiopurines (2–2.5 mg/kg body weight) was introduced. Tcl was given orally, initially 0.05 mg/kg divided in two doses, aiming for serum trough levels of 7–12 ng/mL. After successful initial rescue treatment with Tcl, maintenance therapy with the same drug was continued. Although Tcl is recommended by ECCO for the treatment of moderate to severe UC,[2] it is still off-label for this indication in Switzerland. Azathioprine at a dose of 2–2.5 mg/kg/day, mercaptopurine at a dose of 1.5 mg/kg/day and methotrexate at a dose 15–25 mg/week subcutaneously were used as a possible concomitant immunomodulator therapy.

2.3. Data collection

Data were obtained by retrospective case-note review between September 2010 and January 2012. For each patient the whole hospital and outpatient medical files were reviewed. Follow up data were completed in February 2013.

The following baseline characteristics were recorded for all patients: age, gender, extension of the disease, course of the disease, median Lichtiger score (modified Truelove & Witts severity index (MTWSI)),[15] concomitant therapy and reasons for discontinuation of the first line rescue therapy. Treatment response was analyzed after 1 year if not colectomized. Clinical response was defined as a Modified Truelove & Witts Severity Index <10 with a minimum decrease of 3 points; remission was <4 points.[16] C-reactive protein (CRP) was measured at the beginning of rescue treatment, at week 6, after 6 months and 1 year. The charts of all patients were followed up and screened for side effects for one year or rescue drug's withdrawal or colectomy.

An adverse event was defined as any significant event (symptom, sickness or biological abnormality) occurring in a patient at any time during the study from the date of rescue therapy induction to the last follow up. During the follow up period we recorded side effects of the rescue treatments after 6 weeks (for the period of the first 6 weeks from induction date), at 6 months (for the period from week 6 to week 26) and at 12 months (for the period from week 26 to week 52).

2.4. Endpoints

The primary endpoint of the study was 12 months colectomy rate from the time point of beginning of therapy with primary, secondary or tertiary rescue regime.

Secondary end points were: 1. the need to change to another rescue treatment during the first year after the induction with a rescue treatment; 2. the corticosteroid free remission rate at 12 months from the beginning of the rescue therapies; 3. the presence of adverse events during a year of follow up.

2.5. Statistics

Categorical data are summarized as the percentage of the groups. All numerical data are expressed as median (±interquartile range (IQR)), since the data were not normally distributed. Multivariate binary logistic regression (backward method) was used to identify the most important predictors of therapy failure or success. Colectomy free survival time was calculated using Kaplan–Meier methods, from the date of rescue therapy induction to the date of colectomy. Probabilities of colectomy free survival were expressed as percentages. The statistical package SPSS v. 20 (Chicago, IL, USA) was used to analyze all data.

2.6. Ethical considerations

The study was approved as a nested project of Swiss IBD Cohort Study by the Ethical Committee in Zürich (for all participating Swiss centers), Switzerland, as well as by local Ethical Committee of University Hospital Zvezdara, Belgrade, Serbia.

3. Results

One hundred and eight patients received 146 rescue therapies. All of them were treated with a first line rescue treatment. Thirty-two patients received a second consecutive rescue therapy and 6 patients had a third line rescue treatment. Out of 146 rescue therapies, 68 patients received IFX, 46 patients ciclosporin and 32 received Tcl. Seventy-six patients (70%) received one rescue treatment, 26 (24%) received 2 sequential rescue therapies and 6 patients (6%) received 3 rescue therapies. The baseline patient's characteristics at the time when the first, second or third line rescue therapy started are shown in Table 1.

3.1. Primary rescue treatment

One hundred and eight patients were initially treated with a single rescue treatment – 54 (50%) patients with IFX, 38 (35%) with ciclosporin and 16 (15%) with Tcl. Forty-three (40%) patients either needed colectomy or another rescue treatment within a year (Fig. 1). Eleven patients (11/108) went to colectomy during the first year of follow up (1 patient on IFX, 7 patients on ciclosporin and 3 given Tcl). Instead of colectomy, 32 non-responding patients (30%) chose to be changed to a second line rescue therapy. These 32 patients were treated as follows: 14 with IFX, 13 with ciclosporin and 5 with Tcl (Fig. 2). Sixty-five patients (60%) achieved and maintained clinical response to the first line rescue treatment over a year (Fig. 1). Among those 65 responders, 38 patients were treated with IFX, 18 with ciclosporin and 9 with Tcl. 15 of 18 (83%) responders to the induction therapy with ciclosporin were switched to AZA within the first 6 months, and successfully maintained during 1 year. All 15 patients were AZA naïve.

Observing the group of 76 patients treated with only one rescue treatment, we found a 12 month colectomy rate of 14.5% (11/76). The probabilities of colectomy free survival were 88.2% after 6 weeks, 88.2% after 6 months and 85.5% after one year. The one year corticosteroid free remission rate was 46% (35/76) in this group [with a median MTWSI of 1 (0–3); and the median CRP of 2 (0–11) mg/L; the median MTWSI dropped from 13 (±4) to 1 (±2) and the CRP from initially 20 (±48) mg/L to 2 (±2) mg/L].

3.2. Secondary rescue treatment

Thirty-two patients, who failed to respond to the first line rescue therapy, were treated with a sequential rescue medication (12 with IFX, 15 with Tcl and 5 with ciclosporin) (Fig. 2). The median duration of first line rescue treatment was 71.0 (6–352) days. The median time between first and second rescue treatments was 21.5 (5–58) days. Of 32 patients, 17 (53%) were primary non-responders to the first rescue therapy, 12 (37.5%) lost response during the time and 3 (9.5 %) of them were changed to the second line treatment due to adverse effects or intolerance to the medication. The details regarding the concomitant medications are shown in

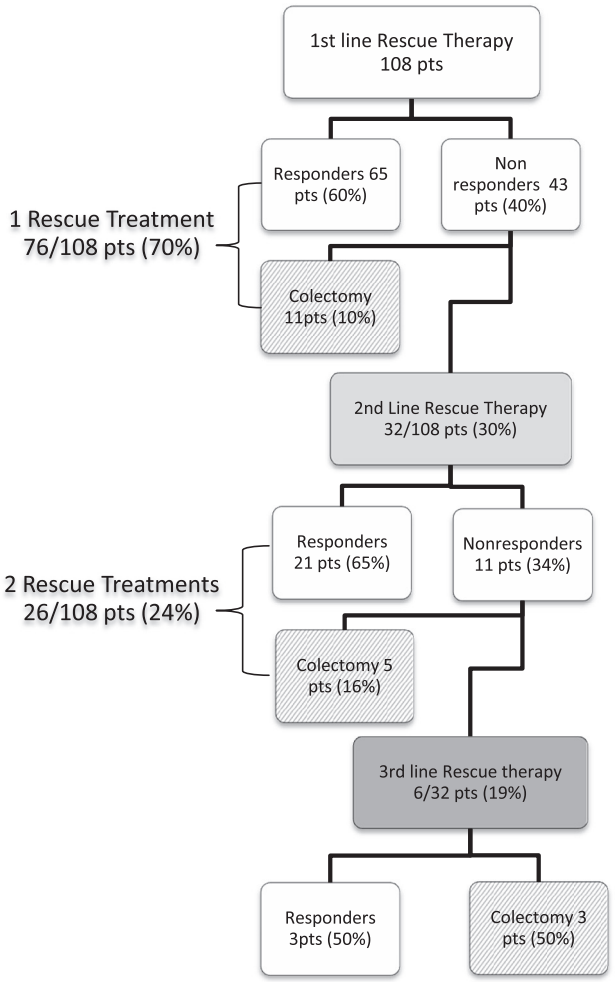

Figure 1 Flowchart of the rescue treatments: colectomy and response rates for the patients with steroid-refractory UC treated with primary, secondary and tertiary rescue treatment.

Table 1. Eleven patients (34%) failed to the second line treatment (Fig. 1). Five of them went to colectomy within the year from the start of the induction with the second rescue treatment (5/32 – 15%).We did not find any differences in colectomy rates between patients who were primary non responders (3/17 – 17.5%) and those who lost response to the rescue treatment (1/12 – 8.3%) (p = 0.535). Instead of colectomy, 6 non-responding patients (6/32 – 19%) received a third line rescue treatment. Twenty-one (65%) patients maintained the clinical response.

In the isolated group of patients treated with only 2 consecutive rescue treatments (26 patients) the one year colectomy rate was 19% (5/26). The probabilities of colectomy free survival were 96.2% after 6 weeks, 92.7% after 6 months and 81% after one year. Among those patients treated with 2 sequential rescue treatments steroid-free remission rate after 12 months was 23% (6/26) [with median MTWSI of 2 (1–3); the median CRP of 1.5 (1–11) mg/L; the median MTWSI dropped from 13 (±5) to 2 (±2) and the CRP from initially 18 (±34) mg/L to 1.5 (±3) mg/L].

3.3. Tertiary rescue treatment

A small group of 6 patients were exceptionally treated with 3 sequential rescue therapies (Fig. 3) in 2 Swiss expert centers (University Hospital Zürich and Tiefenau Spital, Bern): initially, 3 patients were treated with IFX and 3 with ciclosporin. After a median time of 53.0 (15–95) days they were switched to second line treatment – 5 patients to Tcl and 1 to IFX. The median interval between 2nd and 3rd rescue therapies was 18.5 (8–50) days. A primary non-response to the rescue treatment in 5 patients (83.7%) and the loss of response in another patient were the reasons for the discontinuation of the first line rescue therapies.

All 6 patients were offered colectomy instead of a third consecutive rescue medication, but all of them chose another medical treatment. The median duration of second line treatment was 76.5 (12–182) days. Primary non-response was the main reason for the change to the third consecutive rescue treatment in 2 patients (33.3%). Three patients (50%) lost response over the time to the second line treatment. Due to severe allergic reaction to IFX, one patient (16.7%) was switched to the third line treatment. The one year colectomy frequency among those treated with 3 sequential rescue treatments was 50% (3/6). Colectomy

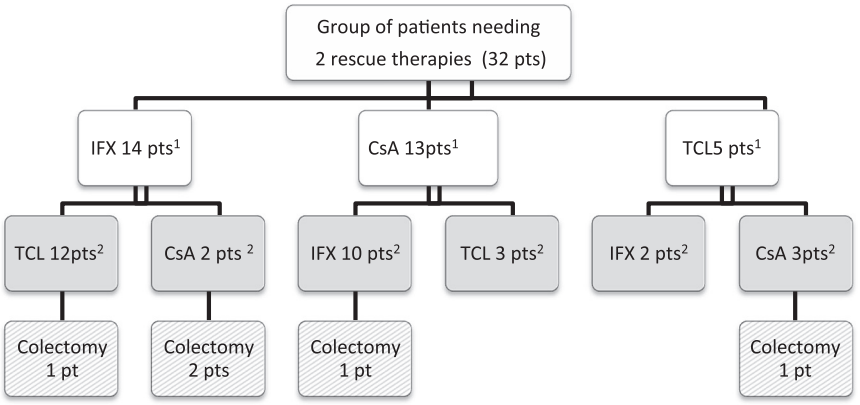

Figure 2 Flowchart of second line rescue therapies: outcome for the group of non-responders to first rescue therapy switched to second line rescue treatment in steroid refractory UC (1/white boxes – primary rescue treatment; 2/gray boxes – secondary rescue treatment).

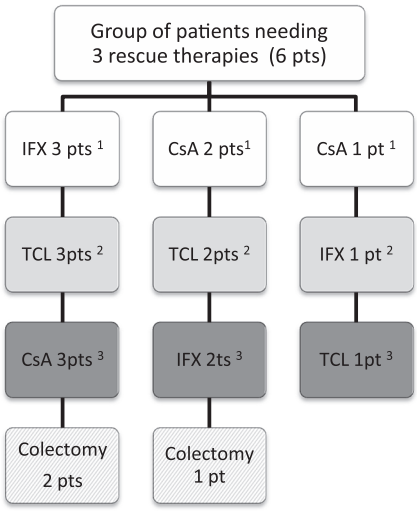

Figure 3 Flowchart of third consecutive rescue treatment: outcome for those patients with steroid refractory UC needing all three consecutive rescue therapies (1/white boxes – primary rescue treatment; 2/light gray boxes – secondary rescue treatment; 3/dark gray- tertiary treatment).

free survival was 83.3% (1/6) at week 6, 83.3% at 6 months and 50% after 12 months. After 12 months only one patient (17%) treated with 3 consecutive rescue therapies achieved remission without steroids [MTWSI – 2; CRP – 1 mg/L; the median MTWSI dropped from 14 (±7) to 2 and the CRP from initially 17 (±66) mg/L to 1 mg/L].

Overall, at the end of follow up in the whole cohort colectomy rate was 18% (19/108) and corticosteroid-free remission rate was 39% (42/108). The univariate analysis showed that the dose of corticosteroids (p = 0.382) and the duration of corticosteroid administration (p = 0.275) did not affect the response (Table 2). Finally, the multivariate analysis indicated that an IFX therapy (p = 0.001) and a shorter duration of disease (p = 0.03) was associated with a better response. A therapy with Tcl and ciclosporin was associated with a worse response than IFX (odds ratio (OR) 3.445 95% CI 1.408–8.429 and OR 4.244 95% CI 1.876–9.599 respectively) (Table 2).

3.4. Postoperative complications in patients who underwent colectomy

No postoperative mortality was found. Considering the early postoperative complications we found one patient with pneumonia (after single IFX rescue treatment), 2 patients

Table 2 Analysis of potential risk factors associated with therapeutic response after 1 year of the rescue treatments.

Candidate risk factor for response	Univariate model		Multivariate model	
	OR, 95% CI	*p*-value	OR, 95% CI	*p*-value
Age	ref.			
	1.008; 0.984–1.033	0.519		
Duration of disease	ref.		ref.	
	0.926; 0.872–0.984	0.013	0.933; 0.876–0.993	0.03
Duration of the latest flair	ref.			
	1.699; 0.527–5.482	0.375		
Severity of disease	ref.			
	0.569; 0.281–1.150	0.116		
Concomitant IMD therapy	ref.			
	0.604; 0.291–1.253	0.176		
Previous IMD failure	ref.			
	1.467; 0.745–2.891	0.268		
Dose of CS therapy	ref.			
	1.014; 0.983–1.046	0.382		
Length of CS therapy	ref.			
	0.994; 0.983–1.005	0.275		
Concomitant treatment with antibiotics (No/Yes)	ref.			
	2.967; 1.130–7.791	0.027		
Hospitalization (No/Yes)	Ref.			
	2.095; 1.064–4.128	0.033		
Rescue therapy (IFX – as reference)				
		0.000		0.001
Rescue therapy Tcl	ref.		ref.	
	3.769; 1.560–9.107	0.003	3.445; 1.408–8.429	0.007
Rescue therapy Ciclosporin	ref.		ref.	
	4.399; 1.978–9.785	0.000	4.244; 1.876–9.559	0.001

First, univariate binominal logistic regression, method enter, was performed, and then the covariates were entered into the multivariate binominal logistic regression model, method stepwise conditional. Abbreviations: CI, confidence interval; OR, odds ratio; IMD, immunomodulators; CS, corticosteroids; IFX, infliximab; Tcl, tacrolimus.

had a wound infection and 2 patients needed a surgical revision (one due to anastomotic stricture, another due to ileus). Considering the long-term postoperative morbidity, we identified 3 patients with chronic pouchitis (12%). The numbers of early postoperative complications do not seem to be increased due to the sequential rescue treatments: 1/3 patients in the group with 3 sequential treatments, 1/5 in the group of patients with 2 sequential rescue treatments and 3/11 in the group with a single rescue treatment. The overall rate of early postoperative complications was 26.3% (5/19).

3.5. Adverse events

In the group of patients treated with the first rescue treatment 36 adverse events (AEs) (36/108 – 33.3%) were found in 25 patients. The most serious problem seen in the study was a cerebrovascular infarction which unfortunately led to death 2 weeks after the ciclosporin introduction (male patient, 52 years old). The patient did not have a history of hypertension. Previous to rescue treatment with ciclosporin he received high doses of intravenous corticosteroids and prophylactic anticoagulation therapy with heparin. It is very likely that cerebrovascular incident was not related to ciclosporin treatment but was a consequence of the fulminant course of disease (CRP 171 mg/L, D dimmer 3421 ng/mL).

Severe allergic reactions, observed in 3 patients in this group, resulted in IFX discontinuation. All others AEs were mild and transitional. The list of adverse events is shown in Table 3. In the group of patients treated with the second line rescue treatments the AEs rate was 37.5% (12 AEs of 32 rescue treatments). Side effects were identified in 8 patients (Table 3).The most serious AEs found in this group were severe allergic reactions, leading to IFX discontinuation, cytomegalovirus (CMV) colitis, resulting in Tcl cessation and transitional renal insufficiency resulting in ciclosporin withdrawal. The others side effects were mild and temporary.

The AE rate after the third line rescue treatment was similar: 30% (2 events in 6 rescue therapies), observed in 2 patients (Table 2). CMV colitis was found in one patient and led to colectomy 32 weeks after the induction of third line rescue treatment.

4. Discussion

Patients with moderate to severe steroid-refractory UC who failed a rescue therapy with either calcineurin inhibitors (ciclosporin, Tcl) or IFX have limited medical options to avoid colectomy at present.

Although a rescue therapy (with IFX after ciclosporin failure, or vice versa) may be associated with higher incidence of complications, many patients prefer to have an additional medical therapy instead of a colectomy. This decision is primarily based on the understanding of the possible complications of J-pouch surgery, including frequent bowel movements, incontinence, and decreased fertility.[17] In many countries the use of a second or even third rescue therapy is uncommon; therefore we aimed to investigate the efficacy and safety of this strategy. Most of our patients were referred to the tertiary centers due to either severe flares of UC or chronically active, refractory disease, seeking to avoid colectomy.

In this study the colectomy rate after the first rescue treatment was 10%, compared to 40% if all non-responders would have been treated by colectomy. However, overall, at the end of follow up, our study showed a colectomy rate of 18% (19/108) in the whole cohort treated sequentially with a first (108 patients), second (32 patients) or third line (6 patients) rescue treatment. Therefore, the second and third-line salvage therapy seems to avoid colectomy. The expected colectomy rate after the first rescue treatment was 40%. Due to the intervention with a second and third line rescue therapy the final colectomy rate was lower (18%) (Fig. 4).

In the literature the long term outcome data for the three medical rescue regimens are discussed controversially: Yamamoto et al.[18] reported a colectomy rate of 27% at 17.5 months in patients with UC treated with Tcl. The long-term efficacy of ciclosporin has been questioned and retrospective analyses have shown increasing colectomy rates up to 60% at 1 year.[19–21] Mocciaro et al. reported one year colectomy rates of 48% and 17% for ciclosporin and IFX respectively,[22] while the Brisbane group showed sustained avoidance of colectomy at 12 months of 42% for ciclosporin and 65% for IFX.[23] Gustavsons and colleagues presented a 50% colectomy free rate for those maintained with IFX after 3 years.[24] The one year colectomy rate in our cohort was slightly lower than 25.6% observed in a recently published Italian study[25] which may related to the fact that 3 different rescue treatments were used and a subgroup in our study was treated with a consecutive 2nd or even 3rd line rescue treatment.

Thirty-two patients who failed to respond to the first line therapy were switched to the second line rescue treatment in our study. After a year of follow up, 11 patients (34%) from this group failed to respond – 5 of them went to colectomy, while 6 others chose to be treated with third line rescue treatment. Due to the exceptional intervention with 3rd line rescue treatment we observed a total of 8 (8/32 – 25%) colectomies within a year and colectomy free survival rate of 75%, instead of 66% in this group. This colectomy free rate in our study seems higher compared to previously reported results in small series: Manosa et al. reported 62% (6/16) colectomy free rate after a median follow up of 195 days.[26] Maser et al. showed that 58% of 19 patients avoided colectomy at 1 year.[9] In the biggest sequential rescue therapy trial, the GETAID group[10] reported a 44% colectomy-free rate within 1 year. A Spanish group[7] recently published a multicenter study including 47 steroid-refractory UC patients treated with IFX salvage therapy after the failure of CsA. They reported one year colectomy rate of 29%, which is similar to the one reported by us. Although, the numbers of treated patients are small, it is very likely that a third line rescue treatment improved our results.

Although we highlighted the significance of avoiding colectomy, it is important to say that a delay of surgery may deteriorate severe disease to a fulminant stage which will be associated with intra- and postoperative complications.[27] We found 26.7% of early postoperative complications which is in accordance with literature.[28,29] A significant increase of postoperative morbidity among those treated with 2 or 3 rescue therapies was not observed in our study. The relatively low rate of surgical complications may reflect

Table 3 List of adverse events in all three groups of patients treated with sequential rescue therapies for steroid refractory UC.

Type of AE	Total of events	1st rescue th	No of events	2nd rescue th	No of events	3rd rescue th	No of events
CVI – death	1	CsA	1		/	/	/
Tremor	9	CsA, Tcl	6	Tcl, CsA	2	Tcl	1
Headache	4	CsA	3	Tcl	1	/	/
Arterial hypertension	3	CsA	2	CsA	1	/	/
Neuropathy	1	CsA	1	/	/	/	/
Paresthesiae of hands	1	CsA	1	/	/	/	/
Anemia	1	Tcl	1	/	/	/	/
Hypertrichosis	3	CsA	2	CsA	1	/	/
Renal abnormalities	3	CsA	2	CsA	1	/	/
Hepatic abnormalities	1	Tcl	1	/	/	/	/
Nausea	1	CsA	1	/	/	/	/
Severe allergic reaction	4	IFX	3	IFX	1	/	/
Allergic reaction	2	IFX	1	/	/	/	/
Erythema of hand and foot	1	IFX	1	/	/	/	/
Atopic dermatitis/skin exanthema	2	IFX	1	IFX	1	/	/
Skin abscess	1	/	/	IFX	1	/	/
Psoriasis	1	IFX	1	/	/	/	/
Hear loss/alopecia	3	IFX	2	Tcl	1	/	/
Lupus erythemathodes	2	IFX	2	/	/	/	/
Infections	3	IFX	2	Tcl	1	/	/
Herpes simplex labialis	1	IFX	1	/	/	/	/
Bronchospasm	1	IFX	1	/	/	/	/
CMV colitis	2	/	/	Tcl	1	IFX	1

Abbreviations: AE, adverse events; Th, therapy; IFX, infliximab; Tcl, tacrolimus; CsA, ciclosporin; CMV, cytomegalovirus.

the fact that all patients were treated and operated in tertiary IBD centers.

Beside the colectomy rate as the most robust end point in retrospective series, we also looked at the one year corticosteroid free remission rate which was 39%. Still, it seems that intervention with 2nd and 3rd line led to a modest improvement of the remission rate: from 32% (35/108) after the first line rescue treatment to 39% (42/108) after sequential salvage therapies. Among the patients who were treated with second (and third) rescue therapies, 22% (7/32) maintained steroid free remission rate over the year, which is similar to the results of a German group[30] who reported 25% one year remission rate in the group of UC patients treated with IFX sequential therapy after Tcl failure. The remission rate in our study is lower compared to Mount Sinai experience[9] who reported 37% remission rate for a median time of 10.4 months. Leblanc and colleagues found 22% of corticosteroid free remission rate within 3 months.[10]

Among 65 responders to the primary rescue treatment, 18 received induction therapy with ciclosporin. 83% (15/18) of them were successfully switched and maintained with AZA during one year. Considering the fact that all of these patients were not treated with AZA previously, our results confirm that ciclosporin is mostly working in AZA naïve patients.

Safety is the most important concern when considering a second and third line rescue therapy in steroid-refractory UC. The consecutive immunosuppressive treatment could be harmful by increasing the risk for infections or by delaying surgery. Toruner and coworkers[31] reported a significantly increased risk of opportunistic infections when adding immunosuppressive therapies on the top of steroid therapies. Maser and coworkers[9] reported a frequency of 16% of severe adverse events in their cohort including one death from gram negative sepsis. The authors suggested checking the IFX serum trough levels before starting ciclosporin, to minimize the likelihood of toxicity; however this has not investigated so far. Herrlinger et al[30] found severe adverse events resulting in IFX withdrawal in 8% patients with UC previously treated with Tcl. The GETAID group found a 22% rate of adverse events (10% with serious infections) including one death. Other groups found similar results.[7,26] In the group of our patients treated with first line rescue therapy we observed 36 AEs (33.3%) in 25 patients. The most serious AE seen in this group was a cerebrovascular infarction which unfortunately led to death 2 weeks after the ciclosporin introduction. Previously, the patient had received high doses of corticosteroids and prophylactic anticoagulation therapy with heparin. It is very likely that this complication was not correlated with ciclosporin treatment, but was a consequence of the fulminant course of the disease, or may be just coincidence. All the other adverse events we observed were not serious (elevation of AST, ALT in patient treated with Tcl, transitional renal insufficiency in 2 patients on ciclosporin, 3 severe allergic reactions resulting in IFX discontinuation).

Considering patients treated with 2 sequential rescue therapies we found an AE rate of 37.5% (12 AEs in 8 patients). The most severe AEs were CMV colitis in patient treated with

Tcl (previously on ciclosporin) and a severe allergic reaction to IFX, both resulted with therapy cessation. Among those treated with 3 consecutive rescue therapies the AE rate was 30% (2/6). Another case of CMV colitis was observed in patient treated with ciclosporin (previously on IFX and Tcl). Overall, most of the AEs were mild and transitional. According to our data a second or third rescue therapy will prevent colectomy; however, especially the calcineurin inhibitors are related to an increased toxicity. Therefore a close monitoring of drug levels and biochemical markers needs to be performed to prevent early toxicity.

Our study has strengths and some method-inherent limitations. Our data reflect a real life experience of tertiary IBD centers. We present our experience with the successive rescue treatments (Tcl, ciclosporin and IFX) in steroid-refractory moderate-to-severe UC in a considerably large cohort. The first limitation is the retrospective, uncontrolled study design. The second is the multicenter character of the study: practice may differ from one to another center regarding the choice of the rescue treatment after the corticosteroid failure, definition of the treatment failure and timing to colectomy. This matters not at least because there is also observer variation in scoring MTWSI. However, it is important to emphasize that patients were treated by experienced physicians in referral centers with a strong adherence to the European Crohn's and Colitis Organization guidelines. Finally, our study was not powered enough to evaluate the best salvage therapy schedule in case of corticosteroid failure. We cannot exclude that the better overall effectiveness and safety profiles to sequential rescue treatments in our study were affected by the fact that the patient population in our study had slightly less severe disease (65% of patients with severe disease in our study) compared to other studies.[7,9,10]

A longer follow-up will be necessary to investigate whether a 2nd and 3rd line therapy will only postpone colectomy and ileal pouch-anal anastomosis (IPAA) and what percentage of patients will remain long-term in remission. It is of importance to note that during the childbearing age of patients with IBD even a postponed colectomy will be of major significance. Sexual dysfunction has been reported in a significant number of patients, while dyspareunia was found in 7–26% patients and impotence in 1.5% after restorative proctocolectomy.[7] The most important concern is the decrease of fertility: a meta-analysis showed almost the triple risk of infertility in women after proctocolectomy and IPAA.[32]

In summary, a second or even third line rescue therapy in steroid-refractory UC patients may reduce the colectomy rate at one year. However, it is important to inform the patients about the moderate likelihood of achieving clinical remission and the risk of cumulative toxicity after sequential rescue therapies.

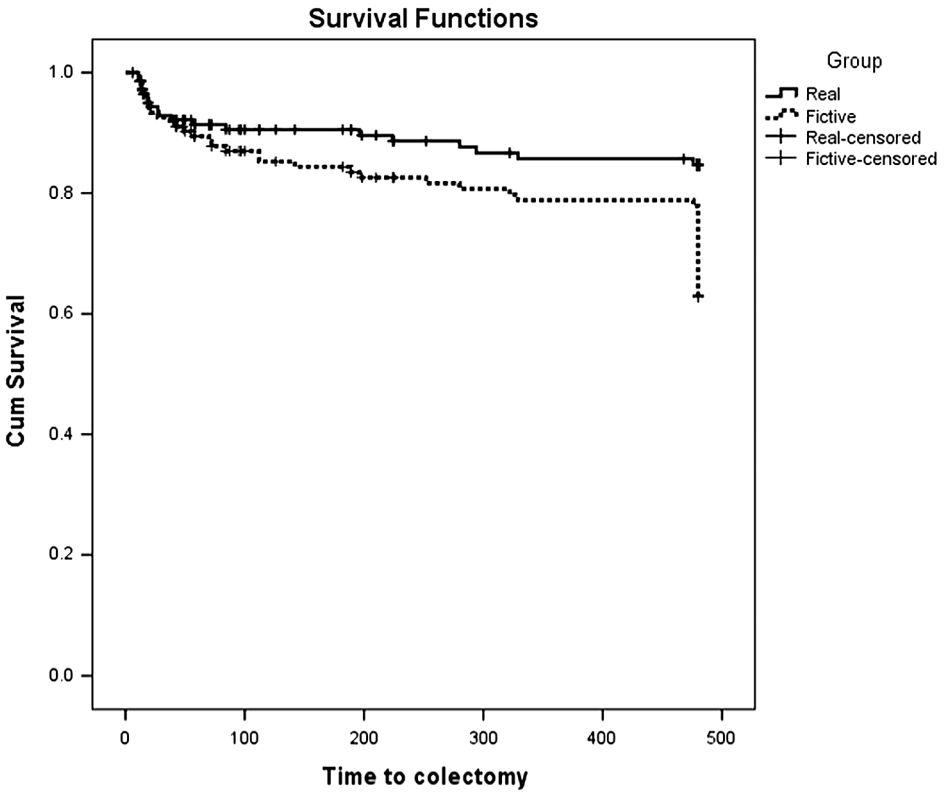

Figure 4 Kaplan–Meier plots show a colectomy free survival for the "real life" cohort (treated with primary, secondary and tertiary treatment) and a fictive cohort (our cohort without intervention with second and third rescue treatment). OR/HR for the fictive group is 2.338 times more than for real group with 95% CI (1.363–4.012); p = 0.002.

Acknowledgments

Specific author contributions:

1. Marijana Protic, corresponding author, contributed equally to this paper as Frank Seibold and made substantial contributions to: conception and design of the study; collecting and validating the data; analysis and interpretation of data; writing the article; drafting the article and revising it critically for important intellectual content; preparing the final version for submission.
   Approved the final draft submitted
2. Frank Seibold contributed equally to this paper as Marijana Protic and made substantial contributions to: conception and design of the study; collecting and validating the data; analysis and interpretation of data; writing the article; drafting the article and revising it critically for important intellectual content; preparing the final version for submission.
   Approved the final draft submitted.
3. Alain Schoepfer contributed to: conception and design of the study; collecting the data; drafting the article and revising it critically for important intellectual content;
   Approved the final draft submitted.
4. Zoran Radojicic performed all statistical analyses and contributed to the drafting of the article and revising it critically for important intellectual content.
   Approved the final draft submitted.
5. Pascal Juillerat contributed to: collecting the data; drafting the article and revising it critically for important intellectual content;
   Approved the final draft submitted.
6. Daniela Bojic contributed to: collecting the data; drafting the article and revising it critically for important intellectual content;
   Approved the final draft submitted.
7. Jessica Mwinyi contributed to: collecting the data; drafting the article and revising it critically for important intellectual content;
   Approved the final draft submitted.
8. Christian Mottet contributed to: collecting the data; drafting the article and revising it critically for important intellectual content;
   Approved the final draft submitted.
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10. Christoph Beglinger contributed to: conception and design of the study; collecting the data; drafting the article and revising it critically for important intellectual content;
    Approved the final draft submitted
11. Stephan Vavricka, conception and design of the study; drafting the article and revising it critically for important intellectual content;
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12. Gerhard Rogler contributed to: conception and design of the study; drafting the article and revising it critically for important intellectual content;
    Approved the final draft submitted
13. Pascal Frei contributed to: conception and design of the study; collecting the data; analysis and interpretation of data; drafting the article and revising it critically for important intellectual content;
    Approved the final draft submitted

Financial support: The study was supported with Swiss National Fond 33CS30-134274.

Potential competing interests: All authors declared - **None**.

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