Alimentary Tract

Outcome of acute severe ulcerative colitis in patients previously exposed to immunosuppressive therapy

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ABSTRACT

Background and aim: We aimed to evaluate the outcome of patients with acute severe ulcerative colitis previously exposed to immunosuppressive (IMS) therapy.
Methods: We retrospectively collected data from 86 consecutive patients from 2008. Early outcome was evaluated as response to steroids, rescue therapy, and colectomy rate, whereas colectomy free-survival was determined along the follow-up.
Results: The overall response rates to steroids and rescue therapy was 33.7% and 90.5%, respectively, while early colectomy rate was 22.1%. Patients previously treated with IMS ($n = 47$) showed a trend towards lower response to steroids (25.5% vs 43.6%; $p = 0.10$), and a high-risk of early colectomy (29.8% vs 12.8%; $p = 0.07$), but a similar response to rescue therapy (87.5% vs 94.4%, $p = 0.62$) when compared with IMS-naïve patients ($n = 39$). The overall cumulative probability to avoid the surgery was 67.5% and 56.6% at 12 and 60 months, respectively, regardless of previous exposure to IMS ($p = 0.30$). At multivariate analysis the risk of early colectomy was increased by previous IMS (OR 5.16, $p = 0.017$), anaemia (OR 4.26, $p = 0.02$), and diagnosis above 40 years (OR 5.31, $p = 0.011$).
Conclusions: Patients previously treated with IMS showed a non-significant trend towards a worse response with steroid therapy, a satisfactory response rate to rescue therapy, and a similar probability of avoiding colectomy during the follow-up vs IMS-naive patients.

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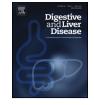
1. Introduction

The management of acute severe ulcerative colitis (ASUC) is still a clinical challenge. Intravenous steroids represent the standard treatment while, in case of failure, a rescue therapy with either cyclosporine (Cys) or infliximab (IFX) can be used with similar efficacy [1]. If rescue therapy fails, colectomy is recommended [2]. Despite the progress in medical therapy, approximately 30% of the patients have to undergo surgery within 3 months after a severe flare of UC [3–5], sometime also due to contraindications of rescue therapy such as in older patients [6].

A variety of predictors of steroid failure have been reported, such as an elevated stool frequency and high C-reactive protein (CRP) levels [7,8], low haemoglobin and serum albumin values [9,10], radiological findings [11,12] and deep ulcerations at endoscopy [13,14].

Few data, however, are available on the outcome of ASUC in patients with previous immunosuppressive (IMS) therapy [15]. The outcome of treating patients already under thiopurine as at the time of admission with Cys seems to be less favourable compared to naïve patients [16]. In addition, previous use of azathioprine (AZA) showed no effect on the outcome of rescue therapy with IFX [17], although data are conflicting [18]. In a retrospective multicenter French study the previous exposure to Cys represented a predictor of colectomy (HR = 2.53; 95% CI = 1.22–5.28), though this study did not include only ASUC [19].

It remains unclear whether previous IMS treatment negatively affect response to steroids, rescue therapy and the need for

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colectomy in patients with ASUC ad this was therefore the aim of the study.

2. Materials and methods

2.1. Patients

We retrospectively collected data from 86 ASUC cases defined according to the Truelove and Witt's criteria [20] consecutively admitted to our Unit from January 2008 to December 2014.

2.2. Management of ASUC

All patients were hospitalized and treated with a short course of high-dose intravenous steroid therapy (metilprednisolone 1 mg/kg/day up to a maximum of 60 mg) and in case of failure they were given a rescue therapy with Cys (2 mg/kg/die in continuous intravenous infusion for 10–14 days) or IFX (5 mg/kg) if colectomy was not deemed necessary [2]. The choice between the two drugs was determined in our cohort by the individual features of each patient (demographic and clinical characteristics, co-morbidities, contraindications, previous treatments). In case of clinical response, intravenous infusion of Cys was shift to an oral formulation (Sandimmun Neoral® at dose of 4 mg/kg/die for 3–6 months) and AZA was quickly added (2–2.5 mg/kg/die), while IFX was continued according to standard criteria (2 and 6 weeks after the first infusion and afterwards every 8 weeks). At admission, all patients underwent a plain abdominal X-ray, lab tests including *Clostridium difficilis* toxins, and a surgical evaluation, which were repeated according to clinical evolution. In addition, all patients underwent a sigmoidoscopy without bowel preparation with rectal biopsies.

2.3. Data collection

For each patient the following data were recorded: gender, age, comorbidity, year of diagnosis, disease extension, disease duration, previous therapy with azathioprine, cyclosporine or Infliximab, concomitant therapy, duration of follow-up, Truelove's criteria. We also collected data of blood test at the time of the admission and endoscopic features, in particular the presence of deep or extensive ulcerations [14].

2.4. End-points

The outcome of ASUC patients was analyzed at discharge from hospital, at one month and at the end of follow up. At discharge we determined the response rate to steroids, rescue therapy and need for colectomy.

Response to steroid was defined as complete resolution of symptoms (clinical remission) or as significant clinical improvement without the need to engage a rescue therapy during the hospitalization. Response rate to rescue therapy was instead defined as the proportion of steroid refractory patients that avoids early colectomy.

During the follow-up period we calculated the overall colectomy rate and colectomy free survival. These evaluations were made in the entire cohort and after stratifying patients on the basis of previous exposure to IMS. Finally, we determined the predictors of response to steroids and the need for colectomy. The role of comorbidity was evaluated using age-adjusted Charlson Comorbidity Index (ACCI) [21].

2.5. Statistic

Data analysis was carried out using Student's t-test, whereas the proportions were analyzed using Fisher's exact test. Kaplan–Meier survival curves for analysis of colectomy free-survival were plotted with the log-rank test. Predictors of steroids response and early colectomy were evaluated by using multivariate logistic regression. Results were expressed as odds ratios (OR) and 95% confidence intervals (95% CI). All tests were two-sided and a p-value <0.05 was considered as statistically significant.

3. Results

3.1. Demographic and clinical characteristic

Demographic and clinical characteristic of the patients are reported in Table 1, while details on previous therapy are given in Table 2.

Table 1
Demographic and clinical characteristics of patients with Acute Severe Ulcerative Colitis.

	All patients	Patients naive to IMS therapy (Group A)	Patients with previous IMS therapy (Group B)	p Group A vs B
N	86	39	47	
Gender				
Male	54	22	32	
Female	32	17	15	0.37
Mean age, yrs (SD)	44.1 (17.1)	47.9 (16.5)	40.9 (17.0)	0.05
Mean disease duration, yrs (SD)	6.4 (7.8)	4.2 (5.2)	8.1 (9.1)	0.02
Extension				
Extensive colitis	72	30	42	
Left side colitis	14	9	5	0.73
CRP, mg/L				
Mean (SD)	51.9 (62.1)	64.0 (69.8)	43.3 (54.2)	
Median (range)	26.5 (5–283)	49 (5–241)	21 (5–283)	0.11
ESR, mm/h				
Mean (SD)	44.87 (23.1)	41.5 (21.5)	47.48 (24.2)	
Median (range)	41 (5–120)	38.5 (7–86)	46 (5–120)	0.25
Deep ulcers [13,14]				
Yes/no	27/44	5/18	22/26	0.06
Therapy at admission				
Azathioprine	25	0	25	NA
Oral steroids	39	21	18	0.19
Charlson index				
Mean (SD)	0.88 (1.38)	1.13 (1.69)	0.68 (1.02)	0.13

IMS, immunosuppressants; SD, standard deviation.