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Acute Severe Ulcerative Colitis: Management and Prognostic Evaluation

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Abstract		**Original Research Article**

Acute severe ulcerative colitis is a serious complication of inflammatory bowel diseases. Its diagnosis is based on clinical and biological criteria. It's management must be quick and multidisciplinary. This work is a retrospective study about 92 cases of acute severe ulcerative colitis collected during a period of 5 years in hepato gastroenterology department of the Mohammed VI University Hospital in Marrakech. The aim of our study is to describe the management of acute severe ulcerative colitis in our context. Acute severe ulcerative colitis accounted for 17% of cases of inflammatory bowel disease. Average age was 28.95 years with a peak of frequency between 21 and 30 years. A slight female predominance was observed (52%). Severe flare was inaugural in 60.8% of cases, the average time for consultation was 22 days. Truelove and Witts criteria were adopted for definition and admission of patients. Endoscopic evaluation showed severity signs in 24% of patients. Intravenous corticosteroid was the first-line therapy in 91 patients (98,9%). Response rate in corticosteroid therapy was 73,6%. Twenty-one patients required oral Ciclosporin as second-line treatment, and 3 patients required Infliximab. Almost half of our patients received an immunosuppressant as a maintenance therapy. Surgery was indicated in 16 cases (17%) including 4 cases who underwent emergency surgery for complications. The overall remission rate of the acute episode was 83% under intensive medical treatment, and 48 % six months after starting maintenance therapy. Mortality rate was 2,2%.

Keywords: Prognostic Evaluation, biological criteria, Intravenous corticosteroid.

INTRODUCTION

Acute severe ulcerative colitis (ASUC) is a medical and surgical emergency which threatens the vital prognosis in short term. It results in the acute inflammation of the colon regardless of the etiology. Even though, inflammatory bowel diseases (IBD) are the main cause of that situation.

It can be the mode of entry into IBD or occur during its evolution [1]. It complicates more particularly the ulcerative colitis (UC) in 15 to 20 % of the cases, but also is observed in low degree during crohn's disease (5 to 10% of the cases) [2].

Its diagnosis is based on the combination of clinical and biological criteria that can be supported by morphological, endoscopic and radiological criteria.

The management of the ASUC is well codified, using IV corticosteroid therapy as a first-line medical treatment. Nevertheless, it is ineffective in one in three patients. Infliximab and ciclosporin can be considered in second line with comparable efficiency and use security; the choice between the molecules must be done case by case. The colectomy has to be proposed from the outset in case of complicated forms and be discussed at each stage of the management, as an alternative to medical treatment.

Our work aims to describe the management of acute severe ulcerative colitis in our context.

PATIENTS AND METHODS
Description of the study

We conducted a retrospective study for descriptive and analytical purposes, including 92 patients, hospitalized for ASUC and treated in the hepato-gastro enterology department of Mohammed VI, the University Hospital of Marrakech, over the cost of 5 years, from 01 January 2013 to 31 December 2017.Were included in our study the cases of ASUC aged between 16 and 75, whose diagnosis was retained on modified Truelove and Witts criteria.

Our data source was:

- Hospital records;
- The medical records of the hepato-gastro-enterology department of the Mohammed VI University Hospital of Marrakech;
- The computerized archiving system;
- The collaboration of the medical and paramedical staff.

Statistical Analyzes

The data entry was done on the Excel software and transferred to the SPSS version 24.0 statistical software.

The descriptive analysis consisted of a calculation of the absolute and relative frequencies for the qualitative variables, and of the positioning and dispersion parameters for the quantitative variables (mean, standard deviation).

RESULTS
Descriptive Study

The ASUC in our series represented 17% (92 cases) in the 541 cases of IBD hospitalized in our hospital during the study period. Seventy-six cases (82%) occurred in the context of ulcerative colitis (UC), 15 (16%) occurred in the Crohn's disease (CD) context, in addition to one case of indeterminate IBD. The average age in our series was 28.95 ± 12.5 years with extremes ranging from 16 years to 75 years. Forty-eight patients (52%) were women, with an average age of 28.95 ± 12.5 years and extremes ranging from 16 to 67 years. The ASUC was inaugural in 56 patients (60.8%), while 36 patients (39.2%) already had a known IBD of which 30 patients had a UC, 5 patients had CD and 1 case of indeterminate IBD. All patients met the criteria of Truelove and Witt, with a median score of 4 (2-5). At the flare-up of the disease, 9 patients were under Thiopurine, 22 patients under 5 ASA and 5 patients did not receive any treatment.

In our series, the average consultation time was 22 days with extremes ranging from 5 days to 45 days.

Rectal bleeding was the main symptom in our patients, because it was noticed in 100% of the patients, and 84.7% of the patients were reported with the impairment of the general condition. The mean hemoglobin (Hb) level was 10.2 g/dl with extremes ranging from 5 to 15.8 g/dl. The mean rate of the erythrocyte sedimentation rate was 59.3 mm/h with extremes ranging from 11 to 126 mm at the 1st hour. Seventy-eight patients (84% of cases) had the erythrocyte sedimentation rate ≥ 30mm at the first hour. The albumin mean rate level was 29.2 g/l with extremes ranging from 11 g/l to 44 g/l. The hypoalbuminemia was observed in 74 patients (80%), including 4 cases of severe hypoalbuminemia with less than 20 g/l. The signs of endoscopic severity were found in 22 patients.

The following tables summarize all epidemiological (Table-1), clinical (Table-2) and paraclinical (Table-3) characteristics.

Table-1: Epidemiological characteristics of studied patients

Factors studied	N ou mean ± standard deviation	%
Number of patients	92	
Middle age (years)	28,95±12	
Sex-ratio M/F et % F	48/44	52
Sex-ratio F/M at UC	43/33	
Sex-ratio M/F at CD	5/11	
Geographic origin		
Rural	40	44
Urban	52	56
Inaugural ASUC	56	60,8
ASUC on known IBD	36	39,7
UC	30	
Crohn	5	
Indetermined IBD	1	
Location of disease in patients with known UC		
Pancolitis	21	
Left Colitis	4	
Distal Colitis	5	
location of disease in patients with known CD		
Ileocolic	2	
Colic	3	
Ongoing treatment in patients with known IBD		
Thiopurine	9	
Mesalazine	12	
Sulfasalazine	10	
No treatment	5	
History of ASUC in known IBD	13	
Other ATCDs:		
Appendectomy	1	
Pulmonary tuberculosis	1	
Bladder Tuberculosis	1	
Smoking	19	
History of familial IBD	2	

Table-2: Clinical characteristics of studied patients

Clinical data	N ou mean ± standard deviation	%
Average time of consultation (d)	22	
Functional Signs		
Rectal bleeding	92	100
Abdominal pain	63	68.4
Koenig's syndrome	1	1.08
Alteration of the general condition	78	84.7
Extra digestive manifestations		
Articular	42	62
Cutaneous	13	19
Ocular	10	16
BMI		
Thinness< 18,5	45	49
Normal body: 18,5 - 24,9	35	38
Overweight: 25 - 29,9	9	10
Obesity : 30 – 34,9	2	2
Severe obesity: 35 - 39,9	1	1
General signs		
Fever	16	17
Tachycardia	30	32
Hypotension	11	20
Anemic syndrome	62	67
Abdominal exam		
Normal	37	40
Sensibility	52	56
Defense	2	2
Hyper tympanism	1	1

Table-3: Para clinical characteristics of studied patients

Factors studied	N ou mean ± standard deviation	%
Hemoglobin rate (g/dl)	10,2	
Hb < 7	11	12
7 ≤ Hb < 10,5	26	28
10,5 ≤ Hb <12	35	38
Hb ≥ 12	20	22
Sedimentation rate (mm/h)	59,3	
ESR<30	15	16
ESR≥30	77	84
C-Reactive Protein (mg/l)	75,5	
Albumin rate (g/l)	29,2	
Albumin≥ 35	18	20
20 <Albumin< 35	70	76
Albumin< 20	4	4
Stool Parasitology		
Normal	32	35
Cystic form of entamoeba histolitica	17	19
Vegetative form of entamoeba histolitica	33	36
Endoscopic signs of severity	22	24

IV corticosteroid was initiated in 91 patients (98.9%) and 24 patients (26.3%) did not respond. The failure of IV corticosteroid was defined by persistent disease activity following IV steroid treatment at a dose of 1mg/kg/day for at least 5 days. Twenty-one patients who did not respond to the IV corticosteroid received oral ciclosporin-based medical treatment, while 3 patients received infliximab (already treated with Azathioprine and stopped by intolerance to the latter). The median time to initiation of oral ciclosporin treatment was 10 days after initiation of IV corticosteroid.

Fifteen out 21 patients (71,4%) responded to oral ciclosporin. The 6 patients who did not respond to oral ciclosporin (28.6%) were colectomized during the first month due to a lack of response (4 cases) or early relapse of disease activity (2 cases).

Three cases had remission with infliximab as a second-line based treatment without surgery.

In our series, 16 patients (17.3%) in total were operated: one case operated immediately for perforation; 9 non-responders to intensive medical treatment based on IV corticosteroids including: one case of massive hemorrhage, 2 cases of colectasia and 6 cases for non-improvement under steroids and inability to procure second-line medical treatment due to cost. Six patients had been operated after failure of second-line treatment with oral ciclosporin.

In our series, the overall remission rate of the acute episode was 83 % under intensive medical treatment, and 48 % six months after starting maintenance therapy. Mortality rate was 2,2 %.

The following table (Table-4) summarizes the therapeutic modalities.

Table-4: Therapeutic modalities of studied patients

	N ou mean ± standard deviation	%
First line medical treatment with IV corticosteroid	91	98,9
Response to IV corticosteroid	67	
Failure of IV corticosteroid	24	
Second line medical treatment with oral ciclosporin	21	23
Response to oral ciclosporin	15	
Failure of oral ciclosporin	6	
Second line medical treatment with oral infliximab	3	3,3
Response to infliximab	3	
Failure of infliximab	0	
Surgery	16	17,5
Surgery first	1	
Failure of first line medical treatment	9	
Failure of second line mecical treatment	6	
Mortality	2	2,2

DISCUSSION

The ASUC is a classic complication of UC and is observed in nearly 20% of the cases [2]. The ASUC can also be observed during CD or infectious colitis.

The historical cohort conducted between 1975 and 1982 by Gustavsson *et al.*, [3] reports a series of 147 patients hospitalized for a flare-up of UC, including 61 cases of severe flare-up giving a rate of 41%, which remains the highest compared to the other studies. In France, the series of Alves *et al*., [4] noted a frequency of 19.5% of ASUC noted in 164 patients with IBD in a period of 20 years.

In our series, ASUC cases represented 17% of all cases of IBD followed in our hospital, the vast majority of which, the inaugural forms as well as forms complicating known IBD occurred in the setting of UC.

In the literature, one in three patients does not respond to IV corticosteroids. This failure of corticosteroids response can be predicted by objective measurements. Thus, Travis *et al.,* [5] studied 49 patients with 51 severe attacks. Thirty-six clinical, laboratory and radiological variables were studied, showing that at the 3rd day of treatment, 85% of patients with more than 8 evacuations / day and/or 3-8 stools / day with a CRP greater than 45 mg/l, do not respond to corticosteroids and have been colectomized.

Mortality due to colectomy increases beyond the sixth day of preoperative hospitalization [2]. The failure of IV corticosteroids must therefore be anticipated, in order to consider either an early colectomy or a second-line treatment that should be started by the fifth day of hospitalization at the latest [2]. This second-line treatment is based on immunosuppressive: Ciclosporin (CsA), Tacrolimus or Infliximab (IFX). Ciclosporin has demonstrated its interest and this is the progress in the management of ASUC, provided that its use is in a specialized environment and under strict medical and surgical supervision [6].

Several randomized trials have tested the efficacy of Ciclosporin in UC. The trial of Lichtiger *et al.*, [10] showed that the ciclosporin induces significantly more remission than placebo (OR 0.18, 95% CI: 0.05-0.64) in steroid-resistant patients. Simon *et al.*, [7] conducted a randomized, controlled double-blind study in which Ciclosporin (4 mg / kg / day) or placebo was administered as a continuous infusion to 20 patients with severe relapses of UC in whom clinical status did not improve after at least 7 days of IV corticosteroids. Eighty-two percent of patients treated with ciclosporin had an average response time of 7 days compared with 0% who received placebo (p <0.001).

Classically, the ciclosporin (Sandimmun®) is administered continuously intravenously at a dose of 2 mg / kg per day, with the aim of effective

ciclosporinemia between 150 and 250 ng / ml [8]. In case of response to intravenous treatment, a relay by oral ciclosporin is then undertaken.

Despite the effectiveness of ciclosporin injection, in our context, it has never been indicated in our patients because it is unavailable in Morocco.

The oral ciclosporin may be an attractive option in patients with ASUC not responding to corticosteroids, particularly those who have difficulty in having the venous route and to avoid the risk of a central venous catheter. The toxicity of the central nervous system has been described with intravenous Ciclosporin [9].

Some teams initially offer oral micro-emulsion treatment with Ciclosporin, at an initial dose of 2 mg / kg per 12 hours and the objective of a circulating residual rate around 100 ng / ml and a peak (2 hours after taking) close to 600 ng / ml [10].

The infliximab has been the first anti-TNF to be initiated in the management of IBD. This molecule can be used as a second-line treatment in place of ciclosporin. The infliximab has been shown to be effective in induction and maintenance therapy of moderate to severe UC, refractory to conventional therapy in two randomized, double-blind, multicentre, phase III essays with placebo (ACT 1 and 2) [11].

ASUC is an emergency that requires tight bonds between medical and surgical teams. Surgery is indicated in emergency before any medical treatment in case of: perforation, colectasis, toxic syndrome or profuse hemorrhage, as well as in case of failure of intensive medical treatment.

Apart from complications, surgery should not be considered as a last recourse but rather as a therapeutic option discussed at each stage of the management of ASUC. It's the treatment that has been successful in reducing ASUC mortality, provided that it is not proposed too later [12]. Surgery was indicated in 17,3% of cases.

CONCLUSION
The ASUC must be rapidly recognized and objectively assessed by clinical and biological parameters. These simple clinical measures should be performed daily to identify patients who will require colectomy as soon as possible. In our study, preliminary results appeared to be quite encouraging with an overall satisfactory response rate to medical treatment (82%) and a mortality rate of 2.1%.

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