Monitoring Of Severe Crohn's Colitis Treated With Intravenous Corticosteroids By C-Reactive Protein: Results Of A Prospective Study

S Ouerdiane, M Serghini, S Karoui, J Boubaker, A Filali

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Abstract

Background: Monitoring an acute severe ulcerative colitis by C-reactive protein (CRP) have a prognostic impact on management and can predict the outcome of patients. However, the role of CRP as a monitoring tool in severe Crohn's colitis is not established.
Aims: To analyse the ability of simple biochemical parameters to predict intravenous glucocorticosteroid (GCS) treatment failure in patients with severe Crohn's colitis; with special interest for the evolution of CRP levels during the first days of treatment.
Material and methods: We include prospectively all patients with severe Crohn's colitis, attested by a CDAI over to 450 points associated with endoscopic signs of severity, and treated by intensive intravenous corticosteroids. All patients had a measure of CRP level before and at day 3 after treatment initiation. Therapeutic failure was defined as a lack of clinical remission or need for surgery within the first 15 days of treatment.
Results: We include 51 patients (17 men – mean age: 31,7 years). Failure of intensive treatment was observed in 16 cases (31%). Predictive factors for treatment's failure were a low CRP level before treatment (44,46 ± 33,4 mg/l vs 116,52 ± 83,28 mg/l; p=0,04), absence of decreasing of ESR and CRP levels more than 50% at the third day (respectively 100% vs 15/35: 43%; p=0,001 and 100% vs 2/19: 10%; p<0,0001). In multivariate analysis, the only independent predictive factor of treatment failure was the absence of the decreasing of CRP level more than 50% at day 3 (p=0,001; adjusted OR [95%CI]: 0.79[0,45-0,9]).
Conclusion: Monitoring a severe Crohn's colitis patients with CRP measurement is helpful to predict the unfavourable outcome and to select the patients in whom a more aggressive medical treatment should be considered at an early stage.

INTRODUCTION

Intravenous corticosteroid is the first line treatment of acute severe colitis in Crohn's disease ([1]). Recently, treatment by intravenous cyclosporine had constituted a great progress in acute colitis management, avoiding early colectomy in 80% of cases ([2]). Nevertheless, few studies analyse predictive factors for poor response to intravenous glucocorticosteroid treatment in inflammatory bowel disease, concerning most of the time ulcerative colitis. The results were discordant ([3,4,5,6,7]).

The aim of our study is to identify predictive factors of poor response to intravenous glucocorticosteroid treatment in patients with acute severe Crohn's disease colitis. This will enable us to define a group of patients in whom a more aggressive medical treatment should be considered at an early stage.

MATERIAL AND METHODS

MATERIAL

All patients admitted for management of acute severe Crohn's colitis between January 1990 and June 2004 were included. A severe episode of Crohn's disease was defined according to the modified Truelove and Witts ([8]) criteria and/or to endoscopic findings classified according to Carbonnel et al. ([9]). Patients who presented with complications (toxic megacolon, perforation, massive bleeding) underwent emergency colectomy without medical treatment were not included in the present study.

METHODS

All patients receive intravenous glucocorticosteroid treatment (hydrocortisone 300 to 400 mg/day) associated with bowel rest, peripheral parenteral nutrition and a triple

intravenous antibiotherapy including cephalosporin, aminoglycoside, and metronidazole.

Surveillance of the patients includes clinical, biological and radiological tools (daily abdominal radiography). An endoscopic control wasn't performed systematically.

CRP and erythrocyte sedimentation rate (ESR) levels were assessed at the 3 rd day after treatment initiation.

Response to intensive intravenous treatment was defined by clinical improvement especially by a decrease in bloody stool frequency. Failure of intensive intravenous treatment was defined as no change of clinical symptoms, deteriorations or complications under treatment.

STATISTICAL ANALYSIS

Clinical data was analyzed by SPSS 8.0. Qualitative variables were compared by chi2 test or Fisher's exact test. Quantitative variables were compared by Student's t test. Univariate analyses were initially performed to identify potential determinants of outcome. Forward stepwise multiple logistic regressions was then employed to identify predictive factors associated with our outcomes. A P -value ? 0.05 was considered for indicating statistical significance.

RESULTS

PATIENT DETAILS

A total of 51 patients (34 female and 17 male) fulfilled the inclusion criteria. The median age at presentation was 31,7 years. All patients were treated with standard medical therapy of intravenous corticosteroids (hydrocortisone 400 mg/day). ESR was assessed at the 3 rd day after treatment initiation in 39 patients (77%). CRP was assessed before starting treatment in 26 (51%) and at day three in 24 (47%) patients.

Figure 1

Table 1 : Patients characteristics

	Number	Percentage (%)
Localization Iléal / colonic	 13/38	 25/75
Mean age (years)	31,7 +/- 10,59 (16 – 66)	-
Men/Women	34/17	66/33
Inaugural severe acute colitis	29	56,8
Previous intake of corticsteroids	9	17,6
Severe colitis diagnosis Clinicobiological Endoscopic Clinicobiological and Endoscopic	 7 8 36	 13,7 15,7 70,5
Fever (temperature > 37°8)	31	60,7
Fistulizing disease	15	30
Small bowel distension on initial X-ray	10	19,6
Number of Truelove and Witts criteria	3,53 +/- 1,04 (1 – 5)	-
Number of bloody stools per 24 hours	7,58 +/- 2,69 (2 – 15)	-
ESR (mm/h)	71,2 +/- 16 (15 -145)	-
Hemoglobine (g/dl)	9,06 +/- 2,58 (2 – 16)	-
Pulse (battements / mn)	96,92 +/- 16,25 (65 – 150)	-
CRP (mg/l) (n = 40)	80,34 +/- 58,34 (7 – 294)	-
Initial colonoscopy	51	100
Deep ulcerations	31	60,8
Mucosal detachment	6	11,7
Mucosal abrasion	14	27,4
Mucosal break	5	9,8
Rectal involvement	20	39,2
Sigmoid involvement	36	70,5
Left colon involvement	41	80,4
Transverse colon involvement	30	58,8
Right colon involvement	20	39,2
Coecal involvement	18	35,3
ESR at day 3	39	76,4
CRP at day 3	24	47
Mean treatment duration (days)	9,66 +/- 3,02 (3 – 20)	-
Mean follow up (months)	40,07 +/- 39,83 (2 – 144)	-

PREDICTIVE FACTORS OF THERAPEUTIC RESPONSE

Response to intensive intravenous treatment was achieved in 35 of 51 patients (69%). Failure of medical therapy occurs in 16 patients (31%). In univariate analysis, parameters predicting failure of medical treatment were the lack of decrease of ESR value by 50% at third day of therapy (p=0,001 OR [IC95%]: 0,46 [0.32 - 0.67]) and the lack of decrease of CRP level by 50% at third day of therapy (p<0,0001 OR [IC95%]: 0.01 [0.02 - 0.30]). In multivariate analysis, the only independent factor predictive of treatment failure found was the lack of decrease of CRP level by 50% at third day of therapy (p=0,001 OR [IC95%]: 0,79 [0.45 - 0.95]).

Figure 2

Table 2 : Predictive factors of therapeutic response (univariate analysis)

	Good response (n = 35)	Poor response (n = 16)	p	OR (IC95%)
Sex (men/women)	11/24	6/10	0,6	0,76 (0,22-2,63)
Localization Ileal / colonic	9/26	4/12	0,9	1,03 (0,26-4,05)
Mean age (years)	32,14 +/- 11,53	30,68+/- 9,24	0,6	-
Inaugural severe acute colitis (yes/no)	21/14	8/8	0,5	1,50 (0,45-4,93)
Previous intake of corticsteroids (yes/no)	6/8	3/5	0,8	1,025 (0,21-7,41)
Severe colitis diagnosis Clinicobiological Endoscopic Clinicobiological and Endoscopic	5/5/25	2/3/11	0,9	-
Fever (temperature > 37°8) (yes/no)	23/12	8/8	0,2	1,91 (0,57-6,38)
small bowel distension on initial X-ray (yes/no)	10/25	0/16	0,06	0,71 (0,57-1,14)
Fistulizing disease (yes/no)	11/24	11/12	0,6	1,37 (0,36-5,22)
Number of Truelove and Witts criteria	3,45 +/- 1,06	3,62 +/- 1,02	0,6	-
VS (mm/h)	76,08 +/- 31,03	66,31 +/-1,02	0,3	-
Hemoglobine (g/dl)	9,62 +/- 2,81	8,50 +/- 2,36	0,1	-
Pulse (battements/mn)	96,97 +/- 14,40	96,87 +/- 18,11	0,9	-
Number of bloody stools per 24 hours	6,91 +/- 3,27	8,25 +/-2,11	0,1	-
CRP (mg/l)	116,52 +/- 83,28	44,16 +/- 33,4	0,054	-
Deep ulcerations (yes/no)	22/14	9/7	0,8	1,16 (0,35-3,86)
Mucosal detachment (yes/no)	4/31	2/14	0,9	0,90 (0,14-5,52)
Mucosal abrasions (yes/no)	11/24	3/13	0,3	1,98 (0,46-8,41)
Mucosal break (yes/no)	3/32	2/14	0,6	0,65 (0,09-8,41)
Rectal involvement (yes/no)	15/20	5/11	0,4	1,65 (0,47-5,76)
Sigmoid involvement (yes/no)	23/12	13/3	0,2	0,44 (0,10-1,86)
Left colon involvement (yes/no)	28/7	13/3	0,9	0,92 (0,20-4,15)
Transverse colon involvement (yes/no)	22/13	8/8	0,3	1,69 (0,51-5,59)
Right colon involvement (yes/no)	13/12	7/9	0,6	0,76 (0,22-2,52)
Coecal involvement (yes/no)	13/22	5/11	0,6	1,30 (0,36-4,58)
Mean treatment duration (days)	10,40 +/- 2,93	8,93 +/- 3,12	0,1	-
ESR decrease (yes/no) N=43	17/15	0/11	0,001	0,46 (0,32-0,67)
CRP decrease (yes/no) N=24	17/2	0/5	<0,0001	0,10(0,02-0,30)

DISCUSSION

Medical treatment failure was observed in 31% of the cases. This result is similar to what is observed in the most recent studies ([7]). Nevertheless, our study is particular in regard of the great number of Crohn's disease patients included comparing to the other studies in the literature, even though the most recent ones ([5], [7]).

The definition of predictive factors for treatment refractoriness is important considering the bad prognosis of acute severe colitis and the increased risk of life-threatening complications due to prolonged corticosteroid treatment ([10]).

Second-line therapy was previously represented by colectomy, currently by intravenous cyclosporine (2 mg/Kg/day) or infliximab (5mg/kg). Cyclosporine proved it's effectiveness in management of severe acute ulcerative colitis ([11]).

Infliximab is approved for the treatment of moderate to severe Crohn's disease, as well as for fistulizing disease ([12]). The efficacy of infliximab has been proven, both in randomized, controlled trials and in the clinical setting and has become a mainstay in the treatment for refractory Crohn's disease

Travis et al. show in their study that the decrease of CRP levels at the 3 rd day after treatment initiation seems to have a strong predictive value of treatment responsiveness ([3]). These results were not confirmed by more recent studies ([5],[7]).

In our study, decrease of CRP level of more of 50% at the 3 rd day of treatment was correlated to a good response of medical therapy. An initially low CRP level had a predictive value for treatment failure. This result wasn't found in other studies, probably due to the lack of studies about Crohn's colitis. Nevertheless, similar result were found by Louis et al. ([13]) studying the response of Crohn's colitis to infliximab. In this study, the patients who respond to infliximab had a raised initial CRP level if compared to the non-responders (16,8mg/l vs 9,6mg/l, p=0,02). In a recent study, CDP-571, a more humanized alpha plus anti-tumor necrosis factor than infliximab, had not shown it's superiority in regard to placebo in patients with a CRP level > 10mg/l ([14]).

In conclusion, our study is the first Tunisian study attempting to assess predictive factors for response to intravenous corticosteroids in acute severe colitis in Crohn's disease. CRP measurement before and at the 3 rd day of treatment initiation had to be systematically done to better identify patients at high risks to resist to corticosteroid treatment and need cyclosporine or colectomy.

CORRESPONDENCE TO

Dr Sami Karoui Department of Gastroenterology A La Rabta Hospital. 1007 Tunis. Tunisia. Tel: +21671578794 Fax: +21671560522 Mail: sami_karoui@fastmail.fm

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Author Information

Soukaina Ouerdiane, M.D
Department of Gastroenterology, A. La Rabta Hospital

Meriem Serghini, M.D
Department of Gastroenterology, A. La Rabta Hospital

Sami Karoui
Professor, Department of Gastroenterology, A. La Rabta Hospital

Jalel Boubaker
Professor, Department of Gastroenterology, A. La Rabta Hospital

Azza Filali
Professor, Department of Gastroenterology, A. La Rabta Hospital