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BRIEF ARTICLE

Clinical outcomes and predictive factors in oral corticosteroid-refractory active ulcerative colitis

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Abstract

AIM: To evaluate the clinical outcomes and prognostic factors after intravenous corticosteroids following oral corticosteroid failure in active ulcerative colitis patients.

METHODS: Consecutive patients with moderate to severe ulcerative colitis who had been treated with a course of intravenous corticosteroids after oral corticosteroid therapy failure between January 1996 and July 2010 were recruited at Severance Hospital, Seoul, South Korea. The disease activity was measured by the Mayo score, which consists of stool frequency, rectal bleeding, mucosal appearance at flexible sigmoidoscopy, and Physician Global Assessment. We retrospectively evaluated clinical outcomes at two weeks, one month, three months, and one year after the initiation of intravenous corticosteroid therapy. Two weeks outcomes were classified as responders or non-responders. One month, three month and one year outcomes were classified into prolonged response, steroid dependency, and refractoriness.

RESULTS: Our study included a total of 67 eligible patients. At two weeks, 56 (83.6%) patients responded to intravenous corticosteroids. At one month, complete remission was documented in 18 (32.1%) patients and partial remission in 26 (46.4%). Eleven patients (19.7%) were refractory to the treatment. At three months and one year, we found 37 (67.3%) and 25 (46.3%) patients in prolonged response, ten (18.2%) and 23 (42.6%) patients in corticosteroid dependency, 8 (14.5%) and 6 (11.1%) patients with no response, respectively. Total 9 patients were underwent elective proctocolectomy within 1 year. The duration of oral corticosteroid therapy (> 14 d *vs* ⩽ 14 d, $P = 0.049$) and lower hemoglobin level (⩽ 11.0 mg/dL *vs* >11.0 mg/dL, $P = 0.02$) were found to be poor prognostic factors for response at two weeks. For one year outcome, univariate analysis revealed that only a partial Mayo score (⩾ 6 *vs* <6, $P = 0.057$) was found to be associated with a poor response.

CONCLUSION: The duration of oral corticosteroid therapy and lower hemoglobin level were strongly associated with poor outcome.

Key words: Clinical outcome; Prognosis; Corticosteroid; Ulcerative colitis

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon with unknown etiology and is characterized by a typical natural course with recurrent flares of mucosal inflammation. About 15% of patients with UC have been reported to have an overall chance of acute exacerbation and require admission to hospital and treatment with systemic corticosteroids[1,2]. Systemic corticosteroids remain as the gold standard treatment of acute moderate to severe UC. However, about 15%-57% of UC patients remain steroid-dependent or refractory even after steroid treatment[3]. Before the mid-1990s, proctocolectomy was the only treatment in steroid-unresponsive UC patients. Recently, intensive drug therapies have been shown to be effective in reducing and delaying the need for colectomy[4,5].

For UC patients who fail to improve with a maximal dosage of 5-aminosalicylic acids, oral steroid therapy should be considered. Moreover, for those who also do not respond to orally administered steroids, hospital admission is usually required for intensive intravenous treatment[6,7]. However, to the best of our knowledge, there has been no published study describing the clinical course of patients with acute attack of UC who were treated first with oral corticosteroids and subsequently with intravenous corticosteroids due to oral steroid failure. Before demonstrating the efficacy of second line drugs, the response and the clinical outcomes of intravenous corticosteroid therapy after oral administration need to be clarified. In addition, identification of early predictors of intravenous corticosteroid responsiveness could facilitate appropriate patient selection and well-timed administration of second line therapies in such UC patients. Clinically, earlier detection of response is important to help estimate risks, benefits, and duration of treatment, as this will enable the use of alternative drugs before complications of long term use of systemic corticosteroids can develop. However, data on predictive response factors of intravenous corticosteroids following oral corticosteroid therapy are lacking.

Here we sought to identify predictive clinical or biological factors associated with intravenous corticosteroid responsiveness in UC patients that initially did not respond to oral corticosteroids, as well as two week, one month, three month, and one year clinical outcomes of such treated patients with acute attack of UC.

MATERIALS AND METHODS

Patients

The clinical records of patients with active UC who were treated with intravenous corticosteroids immediately after treatment failure of oral corticosteroids at the Yonsei University College of Medicine, Seoul, South Korea between January 1996 and July 2010 were retrospectively evaluated. The diagnosis of ulcerative colitis was based on the accepted clinical, endoscopic, and histopathological criteria[8]. The criteria for eligibility were male or female patients with a diagnosis of UC followed regularly for at least 1 year. The exclusion criteria were patients with a history of corticosteroid therapy at other hospitals, corticosteroid use for diseases other than UC and a follow-up duration of less than 1 year. All enrolled patients were initiated intravenous corticosteroid therapy after admission after failure of oral steroid therapy which was done at outpatient clinic.

Intravenous corticosteroid therapy was initiated with intravenous administration of 100 mg of hydrocortisone every eight hours. Intravenous corticosteroid therapy was continued for 1-2 wk, with the treatment duration depending on the individual patient conditions, followed by gradual tapering of corticosteroids. After clinical improvement of UC, the dose of intravenous hydrocortisone was reduced to 200 mg daily. If the patients had no clinical exacerbation of UC, they were administered 30 mg/d of oral corticosteroid therapy before discharge. Our oral corticosteroid tapering policy was to reduce prednisolone by 5 or 10 mg weekly for patients with improved clinical symptoms but to sustain the current dose of prednisolone for one week for patients with lasting clinical symptoms[9,10]. All patients who were concomitantly taking sulfasalazine (2-4 g/d) or mesalamine (1.5-4 g/d) at the time of flare up continued therapy. Patients who took immuomodulators at the time of acute flare up also maintained their initial immuomodulator therapy while taking corticosteroids.

Our study is a retrospective study from a prospectively collected database. The data are stored in a form of Assess file as well as paper form. After then, the questionnaire including Mayo or partial Mayo scores including Physician Global Assessment (PGA) is updated every visit of the patient to outpatient clinics.

The disease activity was measured by the Mayo score, which consists of stool frequency, rectal bleeding, mucosal appearance at flexible sigmoidoscopy, and PGA[11,12]. Each component was scored 0 to 3 points, and the total score ranged from 0 to 12 points. However, a measurement of this score necessarily requires invasive flexible sigmoidoscopy, which limits repeated measurement. Therefore, most actual disease activity was measured on a nine-point partial Mayo score, which excluded the mucosal appearance at endoscopy[13]. At the initiation of oral corticosteroid therapy, demographic data including age, age at diagnosis, duration, gender, number of acute attacks, extent of disease, concomitant medications, duration of oral corticosteroid therapy, Mayo score, and partial Mayo score were collected. Partial Mayo score and laboratory parameters were also recorded at two weeks, one month, three months, and one year after the time of initiation of intravenous corticosteroid therapy. This study was approved by the institutional board of Severance Hospital.

Definitions

Clinical outcome was measured at two weeks, one month,

three months, and one year after the initiation of intravenous corticosteroids. The classification of response to intravenous corticosteroid therapy was adopted from previous studies with minor modification[3,11,14,15]. Patients at two weeks were classified as responders or non-responders. Non-responder of intravenous therapy after oral corticosteroid therapy was defined as persistent active disease despite administration of intravenous corticosteroids over two weeks, death due to UC attack before day 14, proctocolectomy before day 14, or secondary alternative drug use such as cyclosporine and infliximab before day 14. Proctocolecctomy was performed when the patient had intractable bloody diarrhea, a continued PGA score of 3, severe anemia, persistent abdominal pain, or severe malnutrition despite intensive medical treatment. One month outcomes were classified as complete remission, partial remission, or refractoriness. Complete remission was defined as a stool frequency ≤ 2/d with no rectal bleeding, stool urgency, fever, or any other systemic symptoms, and a PGA score of 0. Partial remission was defined as stool frequency ≤ 4/d or ≤ 50% of initial stool frequency with regression of other clinical symptoms and a PGA score of 1 or 2. Refractoriness was defined as persistent active status despite administration of prednisolone up to 30 mg/d or the equivalent dose over the period of four weeks[14]. Three month outcomes were classified into prolonged response, steroid dependency, and refractoriness. Prolonged response was defined as sustained complete or partial remission during the planned dose reduction or after the completion of corticosteroids[3]. Steroid dependency was defined as need for the same corticosteroid dose for more than two weeks despite clinical improvement, requiring an increased dose, or restarting corticosteroid therapy within two weeks because of exacerbation of symptoms[11,14]. Refractoriness was defined as no improvement of clinical symptoms despite continued corticosteroid use. Similarly, outcomes at one year were subdivided into three groups. Prolonged response was characterized by two conditions: maintaining complete or partial remission after discontinuation of corticosteroid therapy and requiring the same dose for more than two weeks or an increasing dose of corticosteroids only in the first three months. Steroid dependency was defined as restart of corticosteroid therapy due to recurrent flare-up of UC after the first three months or being unable to reduce prednisolone to 10 mg/day within three months. Non-response was defined in the same way as for the intermediate outcomes.

Statistical analysis

Continuous variables were presented as the mean ± SD or median (range) and were compared using two-sample *t* tests. Categorical variables were compared by χ^2 tests or Fisher's exact test. Logistic regression analysis was performed to identify predictive variables of clinical outcomes. *P* values less than 0.05 were considered statistically significant. All the statistical analyses were performed using the statistical software package SPSS 12.0 for Windows (SPSS Inc., Chicago, IL).

Table 1 Baseline characteristics of patients with active ulcerative colitis receiving intravenous corticosteroids after oral corticosteroid therapy failure

	Total patients (*n* = 67)
Gender (male/female)	39/28 (58.2/41.8)
Age (yr)	35 (13-78)
Age at diagnosis (yr)	31 (11-78)
Disease duration (mo)	24 (0-132)
Disease extent	
Proctitis	5 (7.5)
Left-sided colitis	21 (31.3)
Extensive colitis	41 (61.2)
First attack of UC	32 (47.8)
Number of previous flares	2 (1-4)
Initial disease activity	
Full Mayo score	9 (5-10)
Partial Mayo score	6 (3-7)
Initial prednisolone dose (mg)	
≥ 30 and < 40	35 (52.2)
≥ 40	32 (47.8)
Duration of oral corticosteroid use (d)	13 (3-50)
Maintenance before flare up	
None/salicylates/azathioprine	6/47/14
Concomitant medications	
Salicylates	53
Azathioprine	14
CRP (mg/dL)	10.9 (0.1-153.0)
ESR (mm/h)	40.0 (3.0-120.0)
Hemoglobin (mg/dL)	11.7 (6.4-16.5)
Albumin (mg/dL)	3.6 (2.3-5.0)

Data are expressed as absolute numbers (percentage) or median. UC: Ulcerative colitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

RESULTS

Patient characteristics

A total of 67 patients, 39 men and 28 women, with active UC were included in this study (Table 1). The median age at diagnosis was 31 years (range: 11-78 years), and median disease duration at the time of oral corticosteroid therapy was 24 mo (range: 0-132 mo). The median length of oral corticosteroid use before intravenous therapy was 13 d (range: 3-50 d). Forty-one (61.2%) patients had extensive disease, and 32 (47.8%) had their first attack of active UC.

Clinical outcomes after intravenous corticosteroid therapy

Clinical outcomes of patients were organized in a flow chart (Figure 1). At two weeks after treatment, 56 (83.6%) patients responded to intravenous systemic corticosteroids. Seven of the 11 non-responders underwent proctocolectomy before day 14. Three patients were treated with an intravenous tumor necrosis factor-α blocker, and one patient was treated with intravenous cyclosporine. At one month after treatment, 18 (32.1%) patients were in complete remission, 26 (46.4%) in partial remission, and 12 (21.5%) had no response. Collectively, 21.5% of

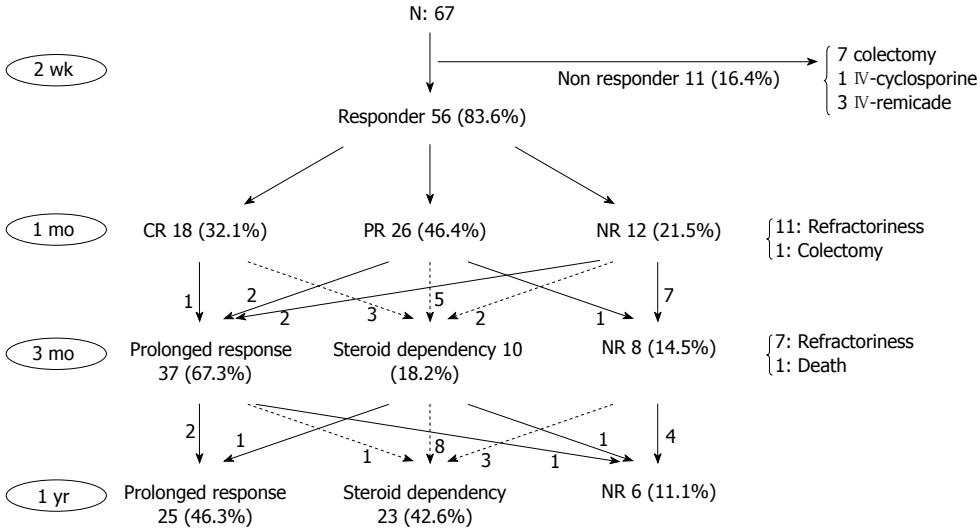

Figure 1 Clinical outcomes of patients with active ulcerative colitis treated with intravenous corticosteroids in oral corticosteroid refractory patients. CR: Complete remission; PR: Partial remission; NR: Non-response.

patients showed treatment failure to systemic corticosteroid therapy, and the other 78.5% of patients showed a partial or complete response to intravenous corticosteroid therapy. At three months, 37 patients had prolonged response, ten had steroid dependency, and seven showed no response. Of the 11 patients who were refractory to corticosteroid therapy at one month, two were in partial remission, two were steroid-dependent, seven had persistent refractoriness at three months, and one patient, a 59-year-old man who underwent proctocolectomy, died of pneumonia and sepsis. At one year, 25 of the 67 patients (37.3%) were categorized with prolonged response, 23 as steroid-dependent (34.3%), and six as non-responders (9.0%).

In our study, cytomegalovirus infection was detected in 5 patients. All were diagnosed by histologic examinations and were treated with ganciclovir. Of these, one patient underwent proctocolectomy within 14 d after the treatment. The rest of them responded to ganciclovir treatment. Finally, three patients were in partial remission and one patient was steroid dependent at one year.

Predictive factors for favorable outcomes

We performed univariate and multivariate analyses to detect clinical or laboratory factors capable of predicting poor outcomes of intravenous corticosteroid therapy after oral corticosteroid therapy failure. For the evaluation of intravenous corticosteroids at two weeks, we divided all patients into two groups: responders and non-responders who experienced death, proctocolectomy, or secondary medical treatment before two weeks. Patients were also divided into good responders and poor responders at one month, three months, and at one year after the corticosteroids therapy: good responders were those who showed a prolonged response, and poor responders were steroid-dependent or non-responsive. Multivariate analysis was carried out using the factors that were found to be statistically significant by univariate analysis.

For two weeks outcomes, univariate analysis of predictors for non-responders showed that disease duration (> 24 mo), duration of oral corticosteroids use (> 14 days), and lower hemoglobin level (≤ 11 mg/dL) were associated with poor prognosis. According to multivariate analysis, the duration of oral corticosteroids use (> 14 d *vs* ≤ 14 d, $P = 0.049$) and lower hemoglobin level (≤ 11.0 mg/dL *vs* > 11.0 mg/dL, $P = 0.02$) remained predictive factors for non-responders (Table 2). No predictive factors for poor responders at one month or three months were identified (Tables 3 and 4). For one year outcome, univariate analysis revealed that only a partial Mayo score (≥ 6 *vs* < 6, $P = 0.057$) was found to be associated with a poor response (Table 5).

DISCUSSION

We analyzed the clinical outcomes and identified predictive factors associated with corticosteroid responsiveness of patients who had an acute attack of UC and had been administered intravenous corticosteroids after a previous course of systemic oral corticosteroid therapy. There have been many previous studies that have reported the predictors of clinical response to systemic corticosteroid treatment in moderate to severe active UC patients[16-19]. However, there are few reports of outcomes of a conservative approach of intravenous steroid treatment in moderate to severe active UC patients after oral corticosteroid therapy failure.

In our study, intravenous corticosteroid therapy following a failure after oral corticosteroid therapy was successful at inducing response at two weeks of treatment in 83.6% of patients. This result implies that intravenous corticosteroids could be administered when a lack of response to oral corticosteroid therapy is shown. This

Table 2 Comparison of clinical factors in immediate outcomes of the two groups of active ulcerative colitis patients receiving intravenous corticosteroids after oral corticosteroid therapy failure

	Responders (n = 56)	Non-responders[1] (n = 11)	P-value		Odds ratio (95%CI)
			Univariate	Multivariate	
Gender (M/F)	32/24 (57.1/42.9)	7/4 (63.6/36.4)	0.690		
Age (yr)	37 (13-78)	39 (29-50)	0.458		
Disease duration (mo)					
≤ 24	34 (60.7)	3 (27.3)	0.041	0.123	3.38 (0.72-15.88)
> 24	22 (39.3)	8 (72.7)			
First attack of UC	26 (46.4)	6 (54.5)	0.273		
Disease extent			0.884		
Proctitis	4 (7.1)	1 (9.1)			
Left-sided colitis	17 (30.4)	4 (36.4)			
Extensive colitis	35 (62.5)	6 (54.5)			
Disease activity					
Full Mayo score (< 9/≥ 9)	27/24 (52.9/47.1)	3/8 (27.3/72.7)	0.122		
Partial Mayo score (< 6/≥ 6)	14/42 (25/75)	1/10 (9.1/90.9)	0.227		
Initial prednisolone dose (mg)			0.622		
≥ 30 and < 40	29 (51.8)	6 (54.5)			
≥ 40	27 (48.2)	5 (45.5)			
Duration of oral corticosteroid use (d)					
≤ 14	33 (58.9)	3 (27.3)	0.054	0.049	4.9 (1.01-23.81)
> 14	23 (41.1)	8 (72.7)			
Concomitant medications			0.809		
Salicylates	44 (78.6)	9 (81.8)			
Azathioprine	12 (21.4)	2 (18.2)			
CRP (mg/dL)					
≤ 8	37 (66.1)	11 (84.6)	0.303		
> 8	19 (33.9)	2 (15.4)			
ESR (mm/h)	40 (3-120)	40 (12-83)	0.999		
Hemoglobin (mg/dL)					
≤ 11	18 (32.1)	8 (72.7)	0.012	0.02	0.16 (0.03-0.75)
> 11	38 (67.9)	3 (27.3)			
Albumin (mg/dL)	3.63 (2.3-5.0)	3.56 (2.8-4.8)	0.331		

[1]Non-responder group included patients that had secondary alternative drug use, proctocolectomy and death before day 14. M/F: Male/female; UC: Ulcerative colitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

result was partly explained by previous pharmacokinetic studies, which demonstrated delayed prednisolone absorption after an oral dose in patients with acute colitis as compared to healthy controls and higher plasma levels after intravenous steroid administration[20,21]. In addition, intravenous steroid administration in the hospital ensures good treatment compliance.

The rate of failure of intravenous corticosteroid therapy in moderate to severe UC attacks was quite high, accounting for 30%-40% in recent studies investigating Western populations[16-19,22,23]. Moreover, Meyers *et al*[24] showed a better clinical improvement of intravenous corticotrophin therapy for acute UC in steroid-naïve patients than in patients who had already received steroid treatment. Considering that our enrolled patients were an oral corticosteroid failure group and approximately half of them were non steroid-naïve patients, our results at two weeks showed a much higher response rate to intravenous corticosteroid therapy compared with previous studies[16-19,22,23]. Moreover, In our study, 13.4% of patients underwent proctocolectomy or experienced death within one year, while the incidence of cumulative proctocolectomy was reported to be about one-fifth that of exacerbation of UC[25-27]. This difference in the results of steroid treatment reaffirms the previous report that UC patients in the Korean population have a lower cumulative probability of proctocolectomy compared to those in Western countries[28,29]. Taken together, these results suggest that Korean patients with UC might have a more favorable prognosis compared to Western counterparts. In order to investigate the clinical application of our results in the treatment of UC patients, further prospective studies are warranted.

One month after the initiation of intravenous corticosteroid therapy, 78.5% of patients (32.1% with complete response and 46.4% with partial response) showed clinical improvement, whereas 42.6% were dependent on steroids at one year. It has been previously reported that 22% of patients in a western study became steroid-dependent[3]. Recently, Yoon *et al*[10] reported that a steroid-naïve Korean UC patient showed a good response to steroid treatment, while 40% of UC patients eventually became steroid-dependent or refractory. Our study showed that the responses to intravenous corticosteroids following a failure after oral corticosteroid treatment were similarly favorable in the short term period. However, more than half of patients eventually became steroid-dependent or refractory in the long term.

Table 3 Comparison of clinical factors in one month outcomes of the two groups of active ulcerative colitis patients receiving intravenous corticosteroids after oral corticosteroid therapy failure

	Good responders[1] (*n* = 44)	Poor responders[2] (*n* = 12)	*P*-value univariate
Gender (M/F)	24/20 (54.5/45.5)	8/4 (66.7/33.3)	0.956
Age (yr)	37 (11-78)	38 (29-59)	0.342
Disease duration (mo)			
≤ 24	25 (56.8)	9 (75)	0.253
> 24	19 (43.2)	3 (3)	
First attack of UC	18 (40.9)	8 (66.7)	0.113
Disease extent			0.943
Proctitis	3 (6.8)	1 (8.3)	
Left-sided colitis	13 (29.5)	4 (33.3)	
Extensive colitis	28 (63.6)	7 (58.3)	
Disease activity			
Full Mayo score (< 9/≥ 9)	23/19 (54.8/45.2)	4/5 (44.4/55.6)	0.574
Partial Mayo score (< 6/≥ 6)	12/32 (27.3/72.7)	2/10 (16.7/83.3)	0.452
Initial prednisolone dose (mg)			0.429
≥ 30 and < 40	24 (54.5)	5 (41.7)	
≥ 40	20 (45.5)	7 (58.3)	
Duration of oral corticosteroid use (d)			
≤ 14	26 (59.1)	7 (58.3)	0.962
> 14	18 (40.9)	5 (41.7)	
Concomitant medications			0.212
Salicylates	33 (75)	11 (91.7)	
Azathioprine	11 (25)	1 (8.3)	
CRP (mg/dL)			
≤ 8	28 (63.6)	9 (75)	0.461
> 8	16 (36.4)	3 (25)	
ESR (mm/h)	40.7 (3-120)	37.2 (12-83)	0.464
Hemoglobin (mg/dL)			
≤ 11	15 (34.1)	3 (25)	0.550
> 11	29 (65.9)	9 (75)	
Albumin (mg/dL)	3.6 (2.3-5.0)	3.45 (2.6-4.8)	0.295

[1]Good responders included patients with prolonged response that maintained complete remission or partial remission after completion of corticosteroid therapy; [2]Poor responders included patients with steroid dependence and non-response. M/F: Male/female; UC: Ulcerative colitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Table 4 Comparison of clinical factors in three month outcomes of the two groups of active ulcerative colitis patients receiving intravenous corticosteroids after oral corticosteroid therapy failure

	Good responders[1] (*n* = 37)	Poor responders[2] (*n* = 18)	*P*-value univariate
Gender (M/F)	21/16 (56.8/43.2)	10/8 (55.6/44.4)	0.933
Age (yr)	35 (13-78)	41 (20-62)	0.146
Disease duration (mo)			
≤ 24	22 (59.5)	12 (66.7)	0.606
> 24	15 (40.5)	6 (33.3)	
First attack of UC	15 (40.5)	10 (55.6)	0.294
Disease extent			0.317
Proctitis	3 (8.1)	1 (5.6)	
Left-sided colitis	9 (24.3)	8 (44.4)	
Extensive colitis	25 (67.6)	9 (50)	
Disease activity			
Full Mayo score (< 9/≥ 9)	20/14 (58.8/41.2)	7/9 (43.8/56.3)	0.318
Partial Mayo score (< 6/≥ 6)	11/26 (29.7/70.3)	3/15 (16.7/83.3)	0.297
Initial prednisolone dose (mg)			0.925
≥ 30 and < 40	19 (51.4)	9 (50)	
≥ 40	18 (48.6)	9 (50)	
Duration of oral corticosteroid use (d)			0.639
≤ 14	23 (62.2)	10 (55.6)	
> 14	14 (37.8)	8 (44.4)	
Concomitant medications			0.180
Salicylates	27 (73)	16 (88.9)	
Azathioprine	10 (27)	2 (11.1)	
CRP (mg/dL)			
≤ 8	24 (64.9)	12 (66.7)	0.895
> 8	13 (35.1)	6 (33.3)	
ESR (mm/h)	36.9 (3-120)	47.6 (6-120)	0.251
Hemoglobin (mg/dL)			
≤ 11	14 (37.8)	4 (22.2)	0.247
> 11	23 (62.2)	14 (77.8)	
Albumin (mg/dL)	3.73 (2.7-5.0)	3.44 (2.3-4.6)	0.082

[1]Good responders included patients with prolonged response that maintained complete remission or partial remission after completion of corticosteroid therapy; [2]Poor responders included patients with steroid dependence and non-response. M/F: Male/female; UC: Ulcerative colitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

Reports evaluating predictive factors for poor clinical outcomes have shown different and controversial results. Some found no predictive factors[15,24,30] while others showed several factors related to clinical outcomes[16-19,22,23]. In our study, the UC duration, the duration of oral corticosteroid use, and lower hemoglobin level were associated with failure of steroid treatment on univariate analysis. Of these variables, only duration of oral corticosteroid therapy and lower hemoglobin level were found to be independently associated with failure of corticosteroid therapy on multivariate analysis. Knowledge of the clinical factors associated with non-response to intravenous corticosteroid therapy after oral therapy may be useful in clinical decision-making. Our study was such an attempt to explain this situation. Our results showing the relationships between simple clinical factors, such as lower hemoglobin or duration of oral steroid use, and intravenous treatment outcome might help in predicting poor responders. Lower hemoglobin level as a risk factor for poor response in our study is in accordance with an earlier reports, which reflects that initial severity of disease might be a significant predictor of poor clinical outcome after steroid treatment[19,31,32]. Also, anemia is a common and important complication of IBD with a prevalence rate ranging from 8.8% to 66.6% in UC patients[33,34]. The quality of life, an ability of work, and cognitive function can be impaired because of anemia in IBD patients[35,36]. Impaired quality of life by anemia in UC patients could influence patient well-being sense and PGA. For this reason, lower hemoglobin level could be a risk factor for poor response in our study. However, none of the previous studies have evaluated duration of oral corticosteroid use before intravenous corticosteroids to predict outcome of corticosteroid therapy in patients with UC. We found that the duration of oral corticosteroid administration was an independent predictor of non-response to intravenous corticosteroid therapy on multivariate analysis in patients with acute exacerbation

Table 5 Comparison of clinical factors in one year outcomes of the two groups of active ulcerative colitis patients receiving intravenous corticosteroids after oral corticosteroid therapy failure

	Good responders[1] (*n* = 25)	Poor responders[2] (*n* = 29)	*P*-value univariate
Gender (M/F)	15/10 (60/40)	16/13 (55/45)	0.721
Age (yr)	35 (16-78)	39 (13-64)	0.445
Disease duration (mo)	30 (0-84)	29 (0-120)	0.325
≤ 24	14 (56)	20 (69)	
> 24	11 (44)	9 (31)	
First attack of UC	9 (36)	15 (51.7)	0.248
Disease extent			0.304
Proctitis	1 (4)	3 (10.3)	
Left-sided colitis	6 (24)	11 (37.9)	
Extensive colitis	18 (72)	15 (51.7)	
Disease activity			
Full Mayo score (< 9/≥ 9)	15/9 (62.5/37.5)	11/14 (44/56)	0.195
Partial Mayo score (< 6/≥ 6)	9/16 (36/64)	4/25 (13.8/86.2)	0.057
Initial prednisolone dose (mg)			0.785
≥ 30 and < 40	13 (52)	14 (48.3)	
≥ 40	12 (48)	15 (51.7)	
Duration of oral corticosteroid use (d)			0.337
≤ 14	17 (68)	16 (55.2)	
> 14	8 (32)	13 (44.8)	
Concomitant medications			0.771
Salicylates	19 (76)	23 (79.3)	
Azathioprine	6 (24)	6 (20.7)	
CRP (mg/dL)			
≤ 8	16 (64%)	19 (65.5)	0.907
> 8	9 (36%)	10 (34.5)	
ESR (mm/h)	34.1 (4-81)	46.3 (3-120)	0.171
Hemoglobin (mg/dL)			
≤ 11	9 (36)	8 (27.6)	0.507
> 11	16 (64)	21 (72.4)	
Albumin (mg/dL)	3.8 (2.7-4.7)	3.57 (2.3-5.0)	0.230

[1]Good responders included patients with prolonged response that maintained complete remission or partial remission after corticosteroid therapy had finished; [2]Poor responders included patients with steroid dependence and non-response. M/F: Male/female; UC: Ulcerative colitis; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

of UC. Patients with UC with more severe disease activity achieved remission less often than who tended to achieve remission earlier[37]. The duration of oral corticosteroid therapy was likely to reflect the severity nature of UC in these non-responding patients. Additionally, prolonged oral corticosteroid therapy might be associated with mortality and morbidity such as infection and sepsis in UC patients undergoing surgery. With regard to the duration of intravenous corticosteroid treatment, the limit of 7-10 d for certifying the criteria of steroid resistance was based on historical series, which showed that the median time of remission of UC was 7.5 d and that prolonged treatment beyond 10 d did not increase the remission rate[37]. In contrast with this point of view, a large retrospective study of single experienced hospital was in favor of more conservative approach, which entered into remission within the 21 d of treatment[38]. Therefore it is difficult to define resistance to corticosteroid which day after treatment is used as a limit marker. None of the previous studies have shown duration of oral corticosteroid administration was an independent predictor of non-response to intravenous corticosteroid therapy. This result demonstrates that optimal timing of intravenous corticosteroids after oral therapy was an important clinical factor of medical treatment response. In other words, use of oral corticosteroids for more than two weeks appears to be less effective in terms of clinical outcome. Additionally, long term oral corticosteroids use could lead to worse clinical outcomes and complications. An extended pre-operative use of steroids might increase the risk of surgical complications[39,40]. UC patients undergoing an elective surgery have been shown to be at an increased risk of postoperative infectious complications in patients treated with corticosteroids[40]. In our study, a total of 9 patients underwent elective proctocolectomy within 1 year. Among of them, one patient died of pneumonia and sepsis after proctocolectomy. Therefore, in the management of UC, the optimal timing of administration of intravenous corticosteroids after oral corticosteroid failure should be determined within two weeks after oral corticosteroid therapy. However, the optimal time limit with oral corticosteroid therapy in the face of response has not been clearly defined by randomized controlled trials. Therefore, large scaled, prospective studies are needed to confirm this result.

Yoon *et al*[10] reported that partial Mayo score was a predictive factor of steroid dependency in steroid-naïve patients with UC. In our study, we also showed that initial higher partial Mayo score might be associated with long term poor prognosis of corticosteroid therapy. Considered overall, the partial Mayo scores could help to predict long term potential corticosteroid dependency or refractoriness in active UC patients who are treated with systemic corticosteroid therapy.

Our study on clinical outcomes and factors for response prediction after intravenous therapy after oral corticosteroids failure in active UC patient has clear clinical significance. There have been no previously published studies describing the clinical course of patients with acute attack of UC who were treated first with oral corticosteroids and subsequently intravenous corticosteroids. This study may provide valuable clinical data that can be used in the management of UC patients receiving oral corticosteroids therapy. Such studies could also be used to suggest optimal timing for administration of intravenous corticosteroids in UC patients who are treated with oral corticosteroids. Moreover, our enrolled UC patients possessed the quality of comparatively homogenous corticosteroid therapy indication and same dose of corticosteroids. These facts might be advantageous in terms of eliminating confounding factors.

There were several limitations in our study. Our study was a retrospective study in a single tertiary hospital. Mucosal healing has emerged as an important treatment goal in UC because evidence is accumulating that it can alter the clinical course of UC. However, evidence of cortico-

steroid's ability to promote mucosal healing is limited. A considerable portion of a period in this study was at moment before mucosal healing has emerged as an emerging parameter in UC. Then we could not evaluate the mucosal healing as a parameter of clinical outcomes in this study. Moreover, our study was not a placebo-controlled comparative study. Finally, the sample size was relatively small.

In conclusion, our study showed that most Korean patients with active UC responded well to intravenous corticosteroid therapy after oral corticosteroid therapy failure. However, a considerable number of patients turned out to be refractory to or dependent on this therapy. The duration of oral corticosteroid therapy and lower hemoglobin level were strongly associated with poor outcome. Further prospective studies are warranted to confirm these results and to determine the optimal timing and dose of corticosteroids.

COMMENTS

Background

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon with unknown etiology and is characterized by a typical natural course with recurrent flares of mucosal inflammation. Systemic corticosteroids remain as the gold standard treatment of acute moderate to severe UC. For those who also do not respond to orally administered steroids, hospital admission is usually required for intensive intravenous treatment. However, there has been no published study describing the clinical course of patients with acute attack of UC who were treated first with oral corticosteroids and subsequently with intravenous corticosteroids due to oral steroid failure.

Research frontiers

This study showed that the duration of oral corticosteroids use (> 14 d *vs* ⩽ 14 d, $P = 0.049$) and lower hemoglobin level (⩽ 11.0 mg/dL *vs* > 11.0 mg/dL, $P = 0.02$) was predictive factors for non-responders. Lower hemoglobin level and duration of corticosteroids may be useful in clinical decision-making as the clinical factors associated with non-response to intravenous corticosteroid therapy after oral therapy.

Innovations and breakthroughs

These results showing the relationships between lower hemoglobin or duration of oral steroid use, and intravenous treatment outcome might help in predicting poor responders. Low hemoglobin level as a risk factor for poor response is in accordance with an earlier report which reflects that initial severity of disease might be a significant predictor of poor clinical outcome. However, none of the previous studies have evaluated duration of oral corticosteroid use before intravenous corticosteroids to predict outcome of corticosteroid therapy in patients with UC. This result demonstrates that optimal timing of intravenous corticosteroids after oral therapy was an important clinical factor of medical treatment response.

Peer review

This paper is well written and the authors highlight the limitation of the study appropriately in their discussion: Retrospective design, not strictly comparative in terms of therapies, and small numbers. Nonetheless, there is an important observation in terms of better management of patients with UC. Some of the findings have been previously reported (low hemoglobin as a risk factor for refractoriness) but it is valuable to see the principles applied to a different population. The comparative data is compelling and statistically significant using appropriate methods. Duration of oral steroid administration may be a very useful predictor of outcome in these cases. The authors are right to emphasize the need for further study in this area.

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