Clinical outcomes and factors for response prediction after intravenous corticosteroid therapy in oral corticosteroid-refractory active ulcerative colitis

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Clinical outcomes and factors for response prediction after intravenous corticosteroid therapy in oral corticosteroid-refractory active ulcerative colitis

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<ABSTRCT>

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PURPOSE: Clinical outcomes and factors predictive of favorable response after intravenous corticosteroids following oral corticosteroid failure have not yet been established in the treatment of moderate to severe ulcerative colitis (UC). We therefore evaluated the outcomes and prognostic factors in UC patients after such therapy.

METHODS: Consecutive patients with moderate to severe UC 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, Korea. We retrospectively evaluated clinical outcomes at two weeks, one month, three months, and one year after the initiation of intravenous corticosteroid therapy.

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, and eight (14.5%) and six (11.1%) patients with no response, respectively. The duration of oral corticosteroid therapy (>14 days, $p<0.049$) and lower hemoglobin level ($\leq$11.0 mg/dl, $p<0.02$) were found to be poor prognostic factors for response at two weeks.

CONCLUSIONS: Our study showed that most Korean patients with active UC responded well to intravenous corticosteroid therapy after oral steroid therapy failure. 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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I. 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 (5-ASA), 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.

II. 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, 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].

Intravenous corticosteroid therapy was initiated with intravenous administration of 100 mg/day of hydrocortisone every eight hours. Intravenous corticosteroid therapy was continued for 1-2 weeks, 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/day 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 does of prednisolone for one week for patients with lasting clinical symptoms[9,10]. All patients who were concomitantly taking sulfasalazine (2-4 g/day) or mesalamine (1.5-4 g/day) 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.

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 (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 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/day 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/day 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/day 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.

Statistics

Continuous variables were presented as the mean (±SD) or median (range) and were compared using two-sample *t*-tests. Categorical variables were compared by Chi-squared 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).

III. 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), and median disease duration at the time of oral corticosteroid therapy was 24 months (range 0- 132). The median length of oral corticosteroid use before intravenous therapy was 13 days (range 3-50). Forty-one (61.2%) patients had extensive disease, and 32 (47.8%) had their first attack of active UC.

Table 1. Baseline characteristics of patients with active ulcerative colitis receiving intravenous corticosteroids after oral corticosteroid treatment fail.

	Total patients (N=67)
Gender (M/F)	39/28 (58.2/41.8)
Age (years)	35 (13-78)
Age at diagnosis (years)	31 (11-78)
Disease duration (month)	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 does (mg)	
≥30 and <40	35 (52.2)
≥40	32 (47.8)
Duration of oral corticosteroid use	13 (3-50)
Maintenance of previous before flare:	
None/Salicylates/azathioprine	6/47/14
Concomitant medications	
Salicylates	53
Azathioprine	14
CRP (mg/dL)	10.9 (0.1-153.0)
ESR (mm/hr)	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 mean.
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate

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 TNF-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 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%).

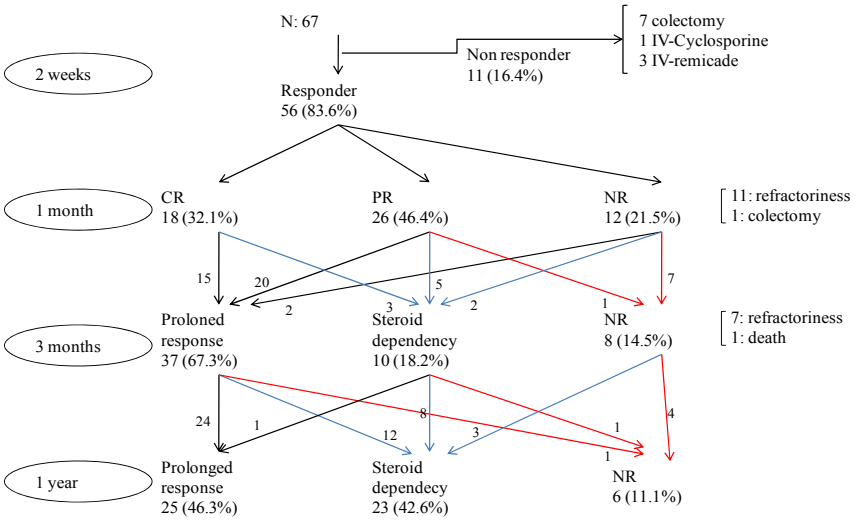

Figure 1. Clinical outcomes of patients with active ulcerative colitis treated with intravenous corticosteroid in oral steroid refractory patients. CR, complete remission; PR, partial remission; NR, non-response.

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 months), 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 days, p=0.049) and lower hemoglobin level (≤11 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 (Table 3, 4). For one year outcome, univariate analysis revealed that only a partial Mayo Score ≥6 (p=0.057) was found to be associated with a poor response (Table 5).

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

	Responders (n=56)	Non responders* (n=11)	Univariate P-value	Multivariate P-value	Hazard Ratio (95% CI)
Gender (M/F)	32/24 (57.1/42.9)	7/4 (63.6/36.4)	0.690		
Age (year)	37 (13-78)	39 (29-50)	0.458		
Disease duration (month)	34 (60.7)	3 (27.3)	0.041	0.123	3.38 (0.72-15.88)
≤24	22 (39.3)	8 (72.7)			
>24					
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)	29 (51.8)	6 (54.5)	0.622		
≥30 and <40	27 (48.2)	5 (45.5)			
≥40					
Duration of oral corticosteroid use (day)			0.054	0.049	4.90 (1.01-23.81)
≤14	33 (58.9)	3 (27.3)			
>14	23 (41.1)	8 (72.7)			
Concomitant medications	44 (78.6)	9 (81.8)	0.809		
Salicylates	12 (21.4)	2 (18.2)			
Azathioprine					
CRP (mg/dL)					
≤8	37 (66.1)	11 (84.6)	0.303		
>8	19 (33.9)	2 (15.4)			
ESR (mm/hr)	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		

* Non-responder group included patients that had secondary alternative drug use, colectomy and death before day 14.

UC, ulcerative colitis

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

	Responders (n=44)	Non responders* (n=12)	Univariate P-value
Gender (M/F)	24/20 (54.5/45.5)	8/4 (66.7/33.3)	0.956
Age (year)	37 (11-78)	38 (29-59)	0.342
Disease duration (month)			
≤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 (day)			
≤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/hr)	40.7 (3-120)	37.2 (12-83)	0.464
Hemoglobin (mg/dL)			
≤11	15 (34.1)	3 (25)	0.55
>11	29 (65.9)	9 (75)	
Albumin (mg/dL)	3.6 (2.3-5.0)	3.45 (2.6-4.8)	0.295

* Good responders included patients with prolonged response that maintained complete remission or partial remission after completion of steroid treatment.

** Poor responder included patients with steroid dependence and non-response.

UC, ulcerative colitis

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

	Good responder* (n=37)	Poor responders** (n=18)	Univariate P-value
Gender (M/F)	21/16 (56.8/43.2)	10/8 (55.6/44.4)	0.933
Age (year)	35 (13-78)	41 (20-62)	0.146
Disease duration (month)			
≤24	22 (59.5)	12 (66.7)	0606
>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 (day)			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/hr)	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

* Good responders included patients with prolonged response that maintained complete remission or partial remission after completion of steroid treatment.

** Poor responder included patients with steroid dependence and non-response.

UC, ulcerative colitis

Table 5. Comparison of clinical factors in one year outcomes of thetwo groups of active ulcerative colitis patients receiving intravenous corticosteroids after orally corticosteroid treatment failure

	Good responder* (n=25)	Poor responders** (n=29)	Univariate P-value
Gender (M/F)	15/10 (60/40)	16/13 (55/45)	0.721
Age (year)	35 (16-78)	39 (13-64)	0.445
Disease duration (month)	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 (day)			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/hr)	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

* Good responders included patients with prolonged response that maintained complete remission or partial remission after steroid treatment had finished.

** Poor responder included patients with steroid dependence and non-response.

UC, ulcerative colitis

IV. 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 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, Meyer *et al*. 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[24]. Considering that our enrolled patients were an oral corticosteroids 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 exacervation 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. Moreover, at one month, complete and partial remissions were observed in 76.5% (44/56) of patients who showed response at two weeks. At

three months, prolonged response was observed in 83.3% (15/18) of patients who showed complete remission, but in 76.9% (20/26) of those who showed partial remission at one month. Prolonged response at one year was observed in 64.9% (24/37) of patients in the steroid response group, but in 10% (1/10) of patients in the steroid dependent group at three months. At the same time, non-response at one month was associated with poor outcomes. At three months, non-response was observed in 58.3% (7/12) of patients who showed no response at one month. At one year, non-response was observed in 50% (4/8) of patients who showed no response at three months. It has been previously reported that 22% of patients in a western study became steroid-dependent[3]. Recently, Yoon *et al.* 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[10]. 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.

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. Low hemoglobin level as a risk factor for poor response in our study is in accordance with some of the earlier reports[19]. 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 of UC. 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. 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.* reported that partial Mayo score was a predictive factor of steroid dependency in steroid-naïve patients with UC[10]. 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. Moreover, our study was not a placebo-controlled comparative study. Finally, the sample size was relatively small.

V. 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.

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< ABSTRACT(IN KOREAN)>

경구 스테로이드치료에 반응이 없는 활동성 궤양성 대장염 환자에서 정주 스테로이드 치료에 대한 임상결과 및 반응 예측인자

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<목적>궤양성 대장염은 원인 불명으로 장에 염증을 일으키며 호전과 악화를 반복하는 만성 염증성 장질환이다. 활동성 궤양성 대장염의 정주 스테로이드 치료시 임상 경과와 예측인자가 많이 알려져 있으나 경구용 스테로이드 치료 실패 후 정주 스테로이드 치료를 시행하는 궤양성 대장염 환자의 경우 임상 결과 및 예측인자가 보고 된 적이 없다. 이에 이러한 치료를 받은 궤양성 대장염 환자에서 임상 경과 및 치료 반응 예측인자를 알아보고자 하였다.

<대상 및 방법> 1996년 1월부터 2010년 7월까지 궤양성 대장염으로 진단받은 환자에서 경구 스테로이드 치료 실패 후 정주 스테로이드 치료를 받은 환자 67명을 대상으로 후향적으로 조사하였다. 질병의 활성도 평가는 Mayo score, Partial Mayo scroe 그리고 혈액 실험 결과를 이용하였으며 경구용 스테로이드 복용시점, 정주 스테로이드 사용 후 2주, 1개월, 3개월, 1년 후에 임상 경과 및 반응 예측인자를 측정하였다.

<결과> 67명의 궤양성 대장염 환자 중 2주 평가 때 56명 (83.6%)이 정주 스테로이드 치료에 반응을 보였다. 정주 스테로이드 치료에 반응이 없는 11명의 환자 중 7명이 전직장결장절제술을 시행받았다. 1개월 평가에서 18명(32.1%)에서 완전 관해, 26명 (46.4%)에서 부분 관해 였으며, 11명(19.7%)은 치료에 반응을 보이지 않았으며 1명이 전직장결장절제술을 시행 받았다. 3개월 및 1년째 평가에서 37명 (67.3%), 25명(46.3%)에서 장기적인 반응을, 10명(18.2%), 23명 (42.6%)에서 스테로이드 의존성을, 8명(14.5%), 6명(11.1%)에서 무반응이 각각 나타났다. 다중 회귀 분석에 의해 경구 치료 기간이 14일 이상 ($p<0.049$)과 낮은 혈색소 (11.0≤/dl),($p<0.02$)가 2주 평가에서 의미 있는 좋지 못한 예후 인자였다.

<결론> 본 연구를 통하여 대부분의 궤양성 대장염 환자는 경구 스테로이드에 치료가 실패하더라도 정주 스테로이드 치료에 단기간 반응은 좋게 나타나지만 상당수에서 장기간 추적 관찰 시 스테로이드 저항 및 치료 실패가 되는 것을 알 수 있었다. 또한 경구 스테로이드의 치료 기간 및 낮은 혈색소 수치는 좋지 못한 예후 인자였다. 이를 임상에 적용하여 환자의 경과를 예측하고 치료하는데 도움이 될 수 있을 것이다.

핵심되는 말 : 임상 결과, 예후, 스테로이드, 궤양성 대장염