Steroid response in moderate to severe pediatric ulcerative colitis: a single center's experience

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Original article

Background: **We aimed to analyze clinical and inflammatory markers of steroid non-response in patients with moderate/severe ulcerative colitis (UC) at the time of diagnosis.**

Methods: **This study included patients who were graded as having moderate/severe UC and received corticosteroids as first-line therapy. Demographic, clinical and laboratory findings and pediatric ulcerative colitis activity scores (PUCAS) were recorded. Response to corticosteroids was assessed 30 days after the induction and long-term therapy.**

Results: **Twenty-eight children were diagnosed as having moderate/severe UC. Their mean age ± SD was 12.2 ± 4 years, and 17% were under 5 years of age. PUCAS at their initial admission was 56.9 ± 11.8. UC was observed at the left colon in 9 patients (32.1%), and pancolitis in 19 (67.9%). At the end of the 30th day, UC was completely remitted in 15 patients (53.5%), partially remitted in 2 (7.1%), and no response in 11 (39.2%). Short-term follow-up showed partial remission in 2 patients, and overall remission with steroid in 17 (60.7%). Non-responders were given second-line treatment; steroid dependency was documented in 2 patients (7.1%) and another 2 (7.1%) patients underwent colectomy. Predictors for steroid non-response were analyzed and only PUCAS at the initial admission was found to be associated with non-response to steroids (51.4 ± 11.4 *vs.* 65.4 ± 6.8, $P<0.05$).**

Conclusions: **Approximately half of the pediatric patients had complete response to steroid therapy in a long period. PUCAS could be used as a potential marker of "failed response" to steroid, but should be supported with a number of prospective randomized controlled studies.**

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Key words: **children; corticosteroid; ulcerative colitis**

Introduction

Corticosteroids are highly effective anti-inflammatory medications that control symptoms of children with moderate to severe ulcerative colitis (UC). The North American Collaborative Registry documented that 87% of newly diagnosed UC patients respond well to first-line therapy with steroids.[1] However, their attendant toxicity circumscribes the use of steroid in the treatment of inflammatory bowel diseases (IBDs). The disease course itself is reported to highly correlate with low bone mineral density in children and adolescents with IBDs, and corticosteroid cumulative dose is suspected as an independent risk factor in this process.[2] Moreover, steroid dependence is reported in up to 30%-40% of patients.[3-5] These documented limitations of the usefulness of steroids point to the need of early parameters for predicting steroid response in children with IBD.

This retrospective analysis of patient profiles aimed to search for clinical and inflammatory markers of steroid non-response in patients with moderate to severe UC at the time of diagnosis.

Methods

This study included patients younger than 18 years who were graded having moderate to severe UC in our pediatric gastroenterology unit and received corticosteroids as first-line therapy. The diagnosis of UC was based on the presence of continuous mucosal disease involving the rectum and extending proximally for variable distances as determined by endoscopy and histological changes consistent with UC.[6]

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Infectious colitis was excluded by stool cultures and histopathological findings. All patients underwent small bowel follow-through examination in order to rule out small bowel involvement. Moderate/severe disease was defined as the occurrence of five or more stools per day, and the daily presence of blood, with or without presence of systemic symptoms.[6,7]

The following variables were recorded from the patient files: demographics, clinical and physical findings at initial examination, laboratory, endoscopy and histology findings, and extent of the disease. The extent of the disease was defined as ulcerative proctitis if the involvement extended to the rectosigmoid region or 20 cm from the anal margin, pancolitis if the involvement extended to the cecum, and left-sided colitis if the involvement was above the rectosigmoid junction without the involvement of the cecum.[8] Pediatric ulcerative colitis activity score (PUCAS) of the patients was recorded and calculated according to the file records at initial admission as defined elsewhere.[9]

Patients were treated with steroids in addition to sulfasalazine or 5-aminosalicylate. Initial dosage of steroids was prednisolone of 2 mg/kg per day (maximum 60 mg/day) or an equivalent dosage given either orally or intravenously. Response to steroid was assessed at 30 days after the induction of therapy and was defined as remission or non-response as follows: (i) remission: regression of clinical symptoms within 30 days with 2 bowel movements per day and no pain, fever or weight loss; (ii) partial remission: regression of symptoms within 30 days with 3-4 bowel movements per day, less abdominal pain, and no fever or weight loss; (iii) non-response: no improvement in clinical and laboratory findings within 30 days.[3] After remission, steroid was tapered and azathioprine was initiated for maintaining remission. A second-line treatment including tacrolimus, infliximab or cyclosporine was initiated in non-responders. Outcome was assessed in a long period (at least 6 months after the first course of steroid therapy) and was defined as a prolonged response, immunosuppression-dependent or others.

For statistical evaluation, SPSS version 10.0 of the package program was used. The Chi-square test and unpaired Student's *t* test were used for comparing variables of the groups, whereas the Mann-Whitney *U* test was used as a nonparametric test. The results were considered statistically significant if $P<0.05$.

Results

Twenty-eight children were diagnosed with moderate/severe UC. The age of the patients (57.1% female) was 12.2 ± 4 years (range: 4 months to 17 years). Seventeen percent of the patients were under 5 years of age. The median duration from onset of symptoms to diagnosis was 5 months. Clinical presentations of the patients are shown in Table 1. The majority of the patients (57.1%) had bloody diarrhea as a major symptom, followed by chronic diarrhea (25.0%). Thirty-five percent (10/28) of the patients had over 10 bowel movements per day, and 53.5% had bowel movements at night. Anemia, thrombocytosis and hypoalbuminemia were found in 71.4%, 53.5% and 75% of the cases, respectively. Acute phase reactants including erythrocyte sedimentation rate and C-reactive protein were increased in 92.8% and 67.5% of the patients, respectively. Perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) was positive in 9 patients (32.1%). Mean ± SD PUCAS at initial admission was 56.9 ± 11.8.

UC was seen in the left colon in 9 patients (32.1%), and pancolitis in 19 (67.8%). Histopathologically, active colitis with cryptitis and/or crypt abscesses was seen in 71.4% and 35.7% of the patients, respectively. All patients had crypt architectural distortion. Mucin depletion and basal plasmacytosis were found in 50% and 42.8% of the patients, respectively. Two patients (7.1%) had pseudo polyp formation and 1 (3.5%) had crypt Paneth cell metaplasia. Backwash ileitis was found in only 1 patient (3.5%).

Outcomes at the end of the 30th day included complete remission in 15 patients (53.5%), partial remission in 2 (7.1%), and no response in 11 (39.2%). Complete remission was achieved in 2 patients with partial remission within 2 months, and the overall remission reached 60.7% in the short-term follow-

Table 1. Clinical and laboratory findings of the patients at initial admission

Parameters	Patients (*N*=28)
Major symptoms, *n* (%)	
Chronic diarrhea	7 (25.0)
Bloody stool	16 (57.1)
Failure to thrive	6 (21.4)
Abdominal pain	3 (10.7)
Severe abdominal pain, *n* (%)	3 (10.7)
Stool at night, *n* (%)	15 (53.5)
Bowel movements >10/day	10 (35.7)
Fever, *n* (%)	16 (57.1)
Joint-related symptoms, *n* (%)	3 (10.7)
Clubbing, *n* (%)	4 (14.2)
Weight and height Z score	-1.9 ± 1.7 and -1.4 ± 0.8
Anemia, *n* (%)	20 (71.4)
Elevated platelets (>400 000/mm^3), *n* (%)	15 (53.5)
Low albumin levels (<3.5 g/dl), *n* (%)	21 (75.0)
High ESR (>20 mm/hr), *n* (%)	26 (92.8)
High CRP (>1 g/dl), *n* (%)	19 (67.5)
Ferritin	37.3 ± 35
p-ANCA (+), *n* (%)	9 (32.1)
PUCAS	56.9 ± 11.8

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ANCA: anti-neutrophil cytoplasmic antibody; p-ANCA: perinuclear anti-neutrophil cytoplasmic antibody.

up. During the follow-up, 4 episodes of relapse were seen in the steroid-response group. In the non-response group, 8 patients received cyclosporine, 2 infliximab, and 1 tacrolimus.

Overall complete remission was achieved in 18 patients [13 (76.4%) of 17 in the response group and 5 (45.5%) of 11 in the non-response group]. Two patients in the early steroid-response group were steroid-dependent (7.1% of all patients and 11.7% of early steroid-responders), and 2 were receiving low doses of steroid due to relapses. Severe, non-responsive disease to second-line therapy was indicated for colectomy in 3 patients with a median interval of 5 months after the diagnosis; 2 (7.1%) of them underwent colectomy but the other one patient refused the procedure and was lost to follow-up. The other 3 patients in the non-response group were still receiving low-dose immunosuppression (partial remission), and none of them experienced side effects of steroids or second-line medications during the treatment (Fig.).

Predictors for steroid non-response were analyzed and only PUCAS at the initial admission was found to be associated with non-response to steroids (51.4 ± 11.4 *vs.* 65.4 ± 6.8, $P<0.05$). No association with the steroid response was determined for the other factors including age, gender, presence of anemia, hypoalbuminemia and thrombocytosis, p-ANCA positivity, erythrocyte sedimentation rate, C-reactive protein, disease extent, and presence of bowel movements at night ($P>0.05$ for all parameters) (Table 2).

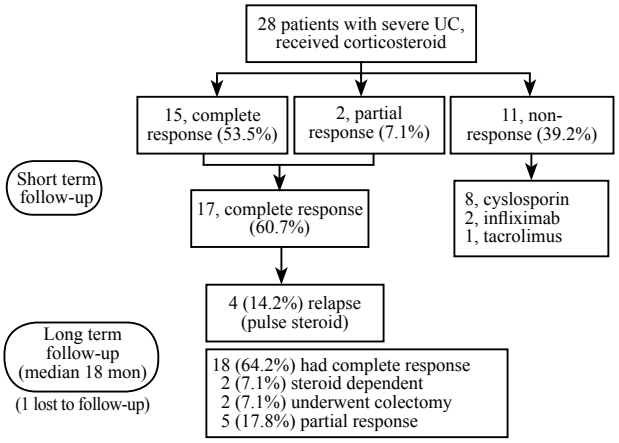

Fig. Outcome of the first line and second line treatment in children with moderate/severe ulcerative colitis (UC).

Discussion

Corticosteroids remain the mainstay of therapy in patients with UC; however, prolonged use of corticosteroids may cause serious side effects such as decrease in growth velocity, osteopenia and metabolic disturbances.[10] In adult patients, immediate response to corticosteroids is common, and long-term corticosteroid dependence and surgery are frequent complications. Childhood IBD and thus UC show some differences from the adult population with respect to clinical presentation and therapeutic consideration. Tung et al[3] examined the early outcome of pediatric patients with IBD after the first course of systemic treatment with steroids, and found that 50% of the patients with UC had complete response whereas 21% had no response.[3] Other reports also supported this observation with early response rates between 50% and 53% in children.[1,11] Our series consisted of selected patients who were graded as having moderate to severe UC and 53.5% of the patients had complete response to steroid in the early period. Steroid dependency developed in 11.7% of responders during the follow-up. These observations may indicate that steroids have comparable effectiveness in severe UC in children.

Predictors of response to first-line steroid treatment have been studied in adult patients previously. Stool frequency of >8/day or 3-8/day and C-reactive protein >45 mg/L on the third day of therapy had a positive predictive value of 85% for colectomy.[12] In children,

Table 2. Analyzing the factors associated with steroid response

Parameters	Response to steroid (n=17)	Failure to steroid (n=11)	Odds ratio (95% CI)
Age, mean ± SD, years	11.5 ± 4.1	13.2 ± 2.9	
Gender (female), *n* (%)	11 (64.7)	5 (45.4)	2.2 (0.36-13.9)
Anemia, *n* (%)	10 (58.8)	10 (90.9)	0.14 (0.01-1.6)
Thrombocytosis (>400 000/mm^3), *n* (%)	9 (52.9)	6 (54.5)	0.94 (0.16-5.5)
Hypoalbunemia (<3.5 g/dL), *n* (%)	14 (82.3)	7 (63.6)	2.6 (0.35-21.8)
ESR (mm/h)	38.7 ± 16.2	42.1 ± 28	
CRP (g/dL)	3.4 ± 2.8	3.7 ± 4.6	
Pancolitis, *n* (%)	14 (82.3)	5 (45.4)	5.6 (0.77-46.5)
p-ANCA (+), *n* (%)	6 (35.2)	3 (27.7)	1.4 (0.21-10.4)
PUCAS	51.4 ± 11.1[a]	65.4 ± 6.8[b]	

$P<0.05$, comparison between *a* and *b*. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; p-ANCA: perinuclear anti-neutrophil cytoplasmic antibody; PUCAS: pediatric ulcerative colitis activity score.

none of the factors such as gender, age at diagnosis, disease duration, and disease extent was found to be associated with the response. Only PUCAS determined at day 3 (>45 points) was found to be associated with "likely to fail" steroid treatment and was recommended for use to introduce second-line therapies on day 5 (>70 points).[11] In our study we found that PUCAS of non-responders were significantly higher on the first day than those of early steroid responders. None of the inflammatory indicators, disease extent or demographic characteristics was correlated with non-response in our study. It is also noteworthy that all surgery-indicated cases had PUCAS over 70 points; however, the colectomy rate of our series was low, prohibiting any statistical correlation.

The limitations of our study are the small number of the study population, which precludes drawing a definitive conclusion, and the retrospective nature of the study. Although PUCAS was higher in non-responders there were still 3 patients in the response group with PUCAS >60. A greater number of patients is needed to make a definitive comment regarding application of PUCAS as a marker of response.

In conclusion, the remarkable findings of our report are: (i) approximately 50% of the patients had complete response to steroid therapy in the long-term, (ii) the colectomy rate was low, and (iii) PUCAS could be used as a potential marker for "failed response" to steroid, but must be supported with large numbers of patients and prospective randomized controlled studies.

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