Response to Induction Therapy in a Pediatric Population of Inflammatory Bowel Disease

Reaktion auf die Induktionstherapie in einer pädiatrischen Population mit chronisch entzündlicher Darmerkrankung

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Schlüsselwörter
- Crohn-Krankheit (Morbus Crohn)
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- Crohn's disease
- ulcerative colitis
- inflammatory bowel diseases
- severity
- treatment

Zusammenfassung

Die Crohn-Krankheit (Morbus Crohn) und die Colitis ulcerosa sind 2 entzündliche Darmerkrankungen, charakterisiert durch eine chronische intestinale Entzündung. In dieser Studie wurden die klinischen Charakteristika einer Gruppe pädiatrischer Patienten mit entzündlicher Darmerkrankung überprüft und ihre Reaktionen auf die Induktionstherapie beurteilt. Für 43 Patienten (20 mit Morbus Crohn und 23 mit Colitis ulcerosa) wurde, gestützt auf die initiale Aktivität, mittels PCDAI und PUCAI die Heftigkeit der Erkrankung bestimmt und die Therapie eingeleitet. Anschließend wurde die Aktivität 6 Monate nach der ersten Diagnose noch einmal überprüft. Die Patienten beider Gruppen litten unter milder bis schwerer Erkrankung. Die durchschnittlichen PCDAI- und PUCAI-Werte betrugen 60,62 ± 16,48 und 50,95 ± 9,35, jeweils für Morbus-Crohn- bzw. Colitis-ulcerosa-Patienten. Die meisten Patienten (83,7%) reagierten auf Standardbehandlungen mit signifikanter Reduktion der PCDAI- und PUCAI-Ergebnisse des Ausgangspunkts (p-Wert < 0,001). Am ursprünglichen Endpunkt von 24 Wochen waren 54% aller Patienten in klinischer Remission; 16 von 23 in der Colitis-ulcerosa-Gruppe (70%) und 6 von 20 in der Morbus-Crohn-Gruppe (30%). Die Ergebnisse dieser Studie geben Klarheit darüber, dass die Einteilung pädiatrischer Patienten mit chronisch entzündlicher Darmerkrankung in unterschiedliche klinische Phänotypen, basierend auf der Aktivität der anfänglichen Symptomatik, Anhalt für ein besseres Management dieser Gruppe liefern und die Nebenwirkungen unnötiger Therapien reduzieren könnte.

Abstract

Crohn's disease (CD) and ulcerative colitis (UC) are two inflammatory bowel diseases (IBD) characterized by chronic intestinal inflammation. In this study, the clinical characteristics of a cohort of pediatric patients with IBD are reviewed and their responses to induction therapy are evaluated. The severity of disease for 43 patients (20 with CD and 23 with UC) was determined using the PCDAI and PUCAI and based on the initial severity, before treatment was started. Following treatment, the severity of disease was re-evaluated at 6 months after the initial diagnosis. The patients in both groups had mild-to-severe disease. The mean PCDAI and PUCAI values were 60.62 ± 16.48 and 50.95 ± 9.35, for CD and UC patients, respectively. Most patients (83.7%) responded to standard treatments with a significant reduction in the PCDAI and PUCAI scores from baseline (p value < 0.001). At the primary endpoint of 24 weeks, 54% of all patients were in clinical remission; 16 of 23 in the UC group (70%) and 6 of 20 in the CD group (30%). The results of this study provide evidence that subgrouping pediatric patients with IBD into distinct clinical phenotypes based on severity of the initial presentation may provide better means of management of this group. This approach can result in a better response to treatment and reduce the side effects of unnecessary therapy.

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Introduction

Inflammatory bowel diseases (IBD) comprise a heterogeneous group of disorders, including Crohn's disease (CD) and ulcerative colitis (UC), that are characterized by chronic intestinal inflammation. Although the etiology is unknown, it seems to result from complex interactions between environmental and genetic factors.

Although IBD can usually be seen in adult ages, approximately 30% of all patients are diagnosed during childhood [1–4]. Many similarities exist between pediatric and adult patients in the nature of the disease, but there are also recognized differences, leading to the discrimination of these two groups. However, there are very limited data on childhood IBD from the developing countries [5–8].

Different treatment modalities have been performed for the induction of remission in these patients. However, most treatment strategies are based on the results obtained from the adult populations and there is a notable paucity of controlled studies in pediatric IBD [9].

Standard clinical outcome measures are mandatory in order to evaluate the outcome of different therapies in IBD children. The pediatric Crohn's disease activity index (PCDAI) and pediatric UC activity index (PUCAI) have become the accepted disease activity measures in childhood IBD, and could be applied in order to assess the response of treatment in the pediatric population [10–12].

Therefore, in the current study, the clinical characteristics of a cohort of pediatric patients with IBD are reviewed and their responses to induction therapy are evaluated using the PCDAI and PUCAI.

Patients and Methods

Study design

In this prospective study, all available pediatric patients who were diagnosed with UC and CD at the Children's Medical Center Hospital [13], Pediatrics Center of Excellence, were enrolled. The study was approved by the regional Ethics Committee of the Hospital, affiliated to Tehran University of Medical Sciences. Inform consent was obtained from either patients or their parents at the time of study.

Following the IBD diagnosis, the severity of disease was determined using the PCDAI and PUCAI and based on the initial severity, treatment was started. For all patients the following regimens were applied: 5-aminosalicylic acid (5-ASA) for mild disease (5 patients) with a starting dose of 20 mg/kg/day and advanced to a final dosage of 70 mg/kg/day, oral steroids (1 mg/kg/day) for moderate disease (25 patients) and steroids plus azathioprine (AZA) (2–2.5 mg/kg/day) or 6-MP (1–2 mg/kg/day) for severe disease (13 patients). Following treatment, the severity of disease was re-evaluated at 6 months after the initial diagnosis.

Subjects

All patients who were <18 years old at the time of diagnosis were investigated in the present study. The following characteristics were investigated at the time of admission: age at presentation, gender, type of IBD, clinical presenting symptoms, extra intestinal manifestations, diagnostic time lag, and severity of disease. All diagnostic work-up data, including the laboratory findings, serological tests, radiological studies, colonoscopic evaluation, and histological findings were obtained.

The diagnosis of IBD was performed according to the Porto diagnostic criteria [14] on the basis of clinical, endoscopic, histopathological and radiological evidence and after exclusion of infection and other recognized causes of inflammation. The diagnosis had to be of at least 6 months' duration. In order to exclude infectious causes of diarrheal illness, stool examinations were performed in all patients. Multiple biopsies were taken from all segments of the gastrointestinal tract during the diagnostic procedure. Patients whose IBD diagnosis was not confirmed by endoscopic or histological examination were excluded from further analysis.

CD was diagnosed when there was evidence of a discontinuous chronic inflammation of the gastrointestinal tract with or without granulomas and supported by clinical, biochemical, and radiological evidence.

UC was defined as endoscopic finding of hemorrhagic-ulcerative inflammation of the rectal mucosa with continuous spreading to the proximal parts of the colon with histological findings of diffuse inflammation limited to the mucosa confirmed by taking multiple colonic biopsy specimens.

Severity assessment

Severity of disease was evaluated at the time of diagnosis for all CD and UC patients using the PCDAI and PUCAI, respectively [10–12]. The PCDAI consisted of three general fields: 1) history, including data regarding abdominal pain, number of liquid stools and patient functioning; 2) physical examination parameters, including abdominal examination, perirectal disease, extraintestinal manifestations, weight, and height; 3) laboratory tests, consisting of hematocrit, albumin, and erythrocyte sedimentation rate. Each item can range on a three-point scale: except for hematocrit and erythrocyte sedimentation rate that are scored as 0, 2.5 or 5 points, others scored as 0, 5, 10 [10, 11]. The PUCAI index was based on six categories, including abdominal pain, rectal bleeding, stool consistency, number of stools per day, any episode of nocturnal bowel movement, and activity level. Each item can range from 0–10 with the exception of rectal bleeding and stools per day which range from 0–30 and 0–15, respectively [12]. PCDAI scores can range from zero to 100, while PUCAI can range from zero to 85.

Following the initial scoring; all patients were subdivided based on their scoring into mild, moderate and severe disease activity. For CD patients; mild disease was defined as the PCDAI score of 10–29, while for scores more than this value, the disease activity was considered moderate to severe. For UC patients; a PUCAI score of 10–29 was considered as mild activity, while cutoff scores for moderate and severe disease were 30 and 65, respectively. Clinical response to treatment required a 25 and 10 points decrease in the PCDAI and PUCAI scores, respectively. Also, clinical remission was defined as a total score of less than 10 for both scales.

Statistical analysis

Data analysis was performed using the SPSS statistical software package, version 14.0 (SPSS Inc, Chicago, IL). A P value of less than 0.05 was considered significant.

Results

Characteristics of patients

There were 43 patients (26 boys and 17 girls); 23 with UC and 20 with CD. There was no difference in the sex distribution between patients with UC and CD (**Table 1**). The median age at onset of symptoms was 8.5 (range: 1 B12) years for all patients, with no significant difference between the two groups. Seventy percent of the children were younger than 10 years at the onset of their symptoms. The median time interval between onset of symptoms and diagnosis was 8 (range: 4 – 18) months. The majority of patients were diagnosed within a year of the onset of their symptoms (16 CD patients, 18 UC). The median age at the time of diagnosis was 10 (range 2 – 15) years for all patients. Considering the site of involvement, the majority of patients with UC had disease affecting both their colon and rectum (82%), followed by left-sided colitis (21%) and proctitis in isolation (7%). In the CD group, the disease was confined to the small bowel in 3 patients (13.3%), the colon in 5 (25%), and affected both areas in 12 (60%).

Table 1 Baseline characteristics of studied patients.

variable	CD (n = 20)	UC (n = 23)
age (mean ± SD)	9.12 ± 3.83	9.15 ± 3.59
sex		
– male	13	13
– female	7	10
presenting manifestation		
– rectal bleeding	19	23
– abdominal pain	1	–
perianal disease	6	3
extra intestinal minifestation		
– hepatobiliary abnormalities	3	3
– arthritis	3	1
– uveitis	1	–

Clinical manifestations

The incidence of perianal disease at presentation in CD was 30% and 13% in UC. Among the extragastrointestinal manifestations observed in our patients, 6 patients (3 CD and 3 UC) suffered from concomitant hepatobiliary abnormalities (13.95%), including 2 UC cases of sclerosing cholingitis, 2 cases of autoimmune hepatitis (1 UC and 1 CD) and 2 CD cases with hepatosplenomegaly. For the patients with sclerosing cholingitis, ursobil was added to the treatment regimen. Meanwhile, 4 patients experienced arthritis (3 CD and 1 UC).

Also one patient in the CD group experienced uveitis during the treatment period. Failure to thrive and growth retardation was a feature in 55% of patients presenting in the CD group.

Response to treatment

At baseline, patients in both groups had mild-to-severe disease as indicated by PUCAI and PCDAI (**Table 2**). The mean PCDAI and PUCAI values were 60.62 ± 16.48 and 50.95 ± 9.35, for CD and UC patients, respectively. In both the UC and CD group, there was not any significant difference between the genders on severity of disease.

Most patients (83.7%) responded to standard treatments with a significant reduction in the PCDAI and PUCAI scores from baseline (p value < 0.001). In only one patient who belonged to the CD group, no reduction in the PCDAI score was observed during treatment.

At the primary endpoint of 24 weeks, 53.5% of all patients were in clinical remission; 16 of 23 in the UC group (69.6%) and 6 of 20 in the CD group (30%). In both CD and UC groups, all patients initially categorized into the mild group were in clinical remission at 24 weeks follow-up; however, for patients suffering from moderate to severe disease, the remission rate was 4 of 18 (22%) and 13 of 20 patients (65%) in the CD and UC groups, respectively.

Adverse effects

There was not any severe adverse reaction to therapy in the studied patients. However, for the patients receiving steroid therapy, acne and cushingoid appearance were documented in 10 and 3 patients, respectively. One patient who was under treatment with AZT had a complication with pancytopenia and therefore the drug was immediately discontinued.

Table 2 Severity of patients during the follow-up period.

variable	CD (n = 20)	UC (n = 23)
baseline		
– mild disease	2	3
– moderate to severe disease	18	20
follow-up		
– mild disease	7	3
– moderate to severe disease	7	4
– remission induction	6	16
response	18	18

Discussion

There are several studies investigating the different treatment options for patients with IBD during the past years. However, the optimal therapy has not been yet established and therefore, different opinions exist for the proper management of these patients [9]. Factors such as disease severity, location, side effects and cost may guide physicians in the care of these patients [14]. In the present study, the severity of disease at presentation was chosen as the single factor in selecting the type of medication.

One of the important issues present in the management of children with IBD is that there are very few clinical trials which have examined the current treatment modalities in the pediatric populations [9, 15]. Also, most doses and dosing intervals have been achieved from studies performed on adults. Since there are unique aspects in the pathophysiology and epidemiology of children with IBD in comparison with adults, such an approach may be problematic. Therefore long-term outcome studies in this age group would be needed in order to identify a definite treatment protocol for this population. In the present study, we aimed to design a treatment algorithm based on the initial severity of the disease in order to optimize the efficacy of our treatment and avoid an increased rate of side effects.

Aminosalicylates are one of the most widely used agents in the treatment of IBD in both the adult and pediatric populations [16, 17]. The effectiveness of these agents has recommended them as the standard induction therapy for UC, with

a clinical effectiveness of about 80% in pediatric patients [16]. However, using these agents to induce disease remission in patients with CD remains uncertain [18]. In the present study, aminosalicylates were administered for both UC and CD with mild disease.

Corticosteroids have been the mainstay in treatment of IBD for many years [19, 20]. They are highly effective in both UC and CD patients and especially for those have been refractory to aminosalicylate therapy. Data collected from the multicenter Pediatric Inflammatory Bowel Disease Registry have indicated the therapy to be effective in most patients treated with steroids with 60% of patients manifesting inactive disease by 3 months postdiagnosis [21]. Also, 50% of the patients were classified as responders and were off steroids altogether within 6 months [21]. In the present study, corticosteroids were administered in isolation and in conjunction with azathioprine for moderate and severe disease activity, respectively.

Immunomodulators such as 6-MP and azathioprine have also been investigated as options for both remission and maintenance therapy. There is evidence indicating a trend toward increasing use of immunomodulation by pediatricians treating patients with IBD [22, 23]. It seems, however, that these agents are administered mostly for maintenance therapy rather than remission induction. A meta-analysis of AZA and 6-MP for the induction of remission in adults has revealed a response rate of 54% for patients with active disease in comparison with a rate of 33% for those on placebo [24, 25]. Although no controlled studies are available for the pediatric population, it seems that such a therapy may not have a significant clinical effect if administered in isolation [26, 27]. In the present study, AZA and 6-MP were coupled with steroids for patients suffering from severe disease. Studies in the adult population have indicated that that treatment with AZA consistently permitted significant steroid reduction compared to placebo [28, 29]. Since the side effects of steroid therapy in the child population such as bone demineralization and growth retardation are of particular concern [30], induction of remission by means of lowering the dosage of steroids could lessen the toxicity of such treatments and improve the quality of life of the children. Therefore we administered the combination of steroids and AZA or 6-MP in order to induce remission with fewer side effects for the most severely affected patients.

In conclusion, the data of this study could provide evidence that subgrouping pediatric patients with IBD into distinct clinical phenotypes based on th eseverity of the initial presentation may provide a better means of management of this group. This approach can result in a better response to treatment and lessen the side effects of unnecessary therapy. However, this conclusion is limited by the fact that there was no control group of not sub-grouped and not treated patients, because keeping the patients untreated is unethical. Indeed although we included all available patients with IBD in this study from main referral center of Iran, the low number of the patients is another limitation of the study. Future studies with a larger number of patients are needed in order to confirm the results of the present study.

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