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ORIGINAL ARTICLE

Retrospective Cohort Study

Histological healing after infliximab induction therapy in children with ulcerative colitis

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Abstract

AIM: To verify the impact of induction therapy with infliximab (IFX) on mucosal healing in children with ulcerative colitis (UC).

METHODS: The study included all UC pediatric patients treated with IFX at our center over the last 10 years. The data were collected from patients' medical charts and analyzed retrospectively. A total of 16 patients with UC underwent colonoscopy with sample collection before and after three IFX injections. Pediatric Ulcerative Colitis Activity Index (PUCAI) was used to assess the clinical condition; endoscopic features were classified according to the Baron scale; and histological changes were evaluated according to the protocol of The British Society of Gastroenterology and Geboes Index. Clinical response was defined as a $\geqslant$ 20-point reduction in PUCAI index, and clinical remission as PUCAI index < 10 points. Endoscopic mucosal remission was defined as completely normal (score 0) on the Baron scale. Histological remission was defined as grade 0 in the Geboes Index. To assess correlation between variables, Spearman's rank correlation coefficient was used.

RESULTS: Clinical remission (PUCAI < 10) at week 8 was achieved in 68.75% of investigated subjects. Endoscopic mucosal remission at week 8 (Baron 0) was observed in 12.5% of patients. Histological remission (Geboes 0) after induction therapy with IFX was noticed in 18.75% cases. A general histological improvement, expressed

by normal surface and crypt architecture, number of crypts, and lamina propria cellularity, was observed in six (37.5%) patients; there was no improvement in nine (56.25%) individuals, and worsening was observed in one (3.75%) case. Changes were not related to UC location. A reduction of inflammatory process was observed in 10 (62.5%) patients; there were no changes in four (25%) individuals, and the inflammation became more severe in two (12.5 %) cases. Simultaneous clinical, endoscopic and histological improvement of parameters assessing disease activity at week 8 was noticed in six (37.5%) patients. 55.5% of investigated patients with normal mucosa seen on endoscopy showed no inflammation on histology. A Baron score of 2 and 3 showed a good correlation with histology results (78.2% of patients with a Geboes Index $\geqslant$ 3).

CONCLUSION: IFX has a positive histological effect in more than one-third of UC patients. IFX reduces intestinal inflammation and improves clinical condition.

Key words: Ulcerative colitis; Endoscopy; Histopathology; Inflammation; Infliximab

Core tip: The impact of infliximab induction therapy on histological healing in pediatric ulcerative colitis (UC) patients is unknown. The present study demonstrates that infliximab induction therapy had a positive influence on histological changes expressed by normal surface, crypt architecture, number of crypts, and lamina propria cellularity in 37.5% of UC patients. The treatment was effective in reducing intestinal inflammation as assessed by the Geboes Index (62.5% of patients). Furthermore, it was shown that there was no significant correlation of histological healing with endoscopic remission and clinical remission.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic idiopathic disease associated with inflammation in the gastrointestinal tract. Traditionally, the goal of the treatment is to reduce symptoms, mainly to induce and maintain clinical remission. New guidelines recommend incorporation of mucosal healing as the primary endpoint of all new clinical trials in patients with UC[1]. In UC (in which lesions are usually limited to the mucosa), mucosal healing should be the ultimate therapeutic goal. However, mucosal healing is not equal to histological healing from the endoscopic point of view. Although infliximab therapy can lead to endoscopically assessed mucosal healing in UC patients[2,3], the evidence of histological outcomes is sparse. A few studies have focused on this subject in adults with UC, but to the best of our knowledge, no data are available for pediatric patients. The aim of this study was to assess mucosal healing in children with UC after infliximab (IFX) induction therapy, especially at the microscopic level.

MATERIALS AND METHODS

Study design

The data were collected from patients' medical charts and analyzed retrospectively. The study included pediatric patients with UC treated with IFX at the Children's Memorial Health Institute in Warsaw, Poland over the last 10 years. All the procedures were reviewed and approved by the Independent Review Board. The patients and their caregivers gave their written informed consent before the start of any procedure.

Only the subjects who received three infusions of IFX and had colonoscopy with collected samples before and after induction with IFX were enrolled. Therefore, seven of 23 UC children treated with IFX during the last 10 years in our center were excluded: in two patients colonoscopy was not performed after the induction therapy; in two patients an adverse reaction occurred after the second infusion; and in three patients IFX therapy was discontinued after the second infusion due to lack of improvement (Figure 1). Eventually, the study included 16 children (7 boys and 9 girls). Diagnosis of UC was established after clinical, radiological, endoscopic, and histological examinations. Patients had moderate to severe UC, either refractory or intolerant to conventional therapy. Data about treatment history (before IFX), concomitant therapies at baseline, and biochemical parameters: hemoglobin, hematocrit, platelet count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) before and after induction, were collected.

Clinical and endoscopic condition

Pediatric Ulcerative Colitis Activity Index (PUCAI) index was used to assess the clinical condition of the subjects[4]. Clinical response was defined as a $\geqslant$ 20-point reduction in PUCAI index, and clinical remission as PUCAI index < 10 points. Endoscopic features were classified according to the Baron scale[5], and mucosal remission was defined as completely normal (score 0). The disease location was classified according to the Paris Classification[6].

Histological features

All patients underwent colonoscopy with sample collection ($\geqslant$ 5 samples) before and after the three IFX

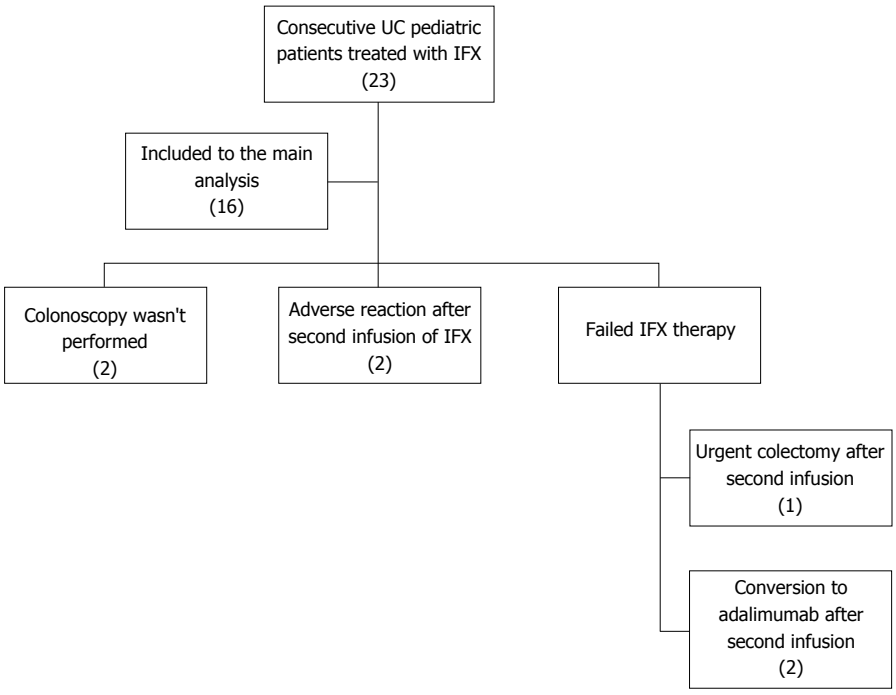

Figure 1 Flow diagram of the study.

injections. Samples were taken from the worst area of inflammation. All specimens were fixed in buffered formaldehyde and embedded in paraffin blocks. Tissue sections, 4 μm thick, were routinely stained with hematoxylin and eosin (HE). Each biopsy specimen was evaluated by two pathologists according to the protocol of The British Society of Gastroenterology[7] and Geboes Index. One of the pathologists has a background in gastrointestinal pathology. Each pathologist evaluated the slices independently. All were blinded to clinical and endoscopic information. For further comparison, in each patient, we chose the samples with the greatest disease activity and histological changes. Histological features were identified and grouped into four main categories: mucosal architecture, lamina propria cellularity, neutrophil polymorph infiltration, and epithelial abnormality.

Mucosal architectural abnormality was indicated by the following: a change in surface topography (flat, irregular or villous), decreased crypt density, and crypt architectural abnormalities (distortion, branching or shortening). Assessment of the abnormal lamina propria cellularity referred to an increase and altered distribution of cell types, and the presence/absence of granulomas and giant cells. The characteristics of UC overlap in the numbers and distribution of neutrophil polymorphs were assessed. Epithelial abnormality included mucin depletion, surface epithelial damage, metaplastic changes, surface intraepithelial lymphocytes, apoptosis, and subepithelial collagen. In each case, the activity of inflammation was additionally evaluated according to Geboes Index, where minimal (grade 1) UC corresponded to any increase in lymphoplasmacytic inflammation in the lamina propria; mildly active (grade 2) UC to granulocytes (neutrophils or eosinophils) confined to the lamina propria; moderately active (grade 3) UC to neutrophils within the epithelium (crypt or surface) without crypt abscesses; and severely active (grade > 3) UC to crypt destruction, erosion or ulceration. Histological remission was defined as grade 0 in the Geboes Index.

Statistical analysis

The frequency of findings was presented as numbers and percentages. All statistical tests were performed with Statistica 10 (StatSoft, Tulsa, OK, United States), package. The Wilcoxon test was used to compare quantitative variables and appropriate χ^2 tests for qualitative variables. To assess correlation between variables Spearman's rank correlation coefficient was used. The threshold of statistical significance was set at $P < 0.05$. The statistical methods of this study were reviewed by Dr Maciej Dadalski form the Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Heath Institute, Warsaw, Poland.

RESULTS

Clinical characteristics

IFX was administered intravenously at 5 mg/kg, as an induction regimen at 0, 2 and 6 wk. The median age at first dose was 13.2 ± 3.1 years (range: 8-17 years). The mean duration of the disease before IFX therapy was 30.3 ± 40.2 mo (range: 1-139 mo). All patients have been previously treated with steroids and aminosalicylate (5-ASA); thiopurines were used in 87.5% of investigated subjects. Eleven patients

Table 1 Characteristics of clinical and biochemical parameters before and after induction therapy with infliximab

Parameter	Week 0				Week 8				*P* value
	mean	Median	Q1	Q3	mean	Median	Q1	Q3	
PUCAI score	49.1	50	35	65	16.3	10	10	20	< 0.05
Body weight (kg)	46.5	44	43	56.6	50.4	53.3	42.7	60.5	< 0.05
Body height (cm)	157.3	163	151	168.5	158.2	163.5	152	170	NS
Hemoglobin (g/dL)	9.9	9.8	8.3	11.3	11	11	10	12.2	< 0.05
Hematocrit (%)	35.8	31.5	29.2	35.8	33.9	34.9	30.1	37.2	NS
Platelet count (K/μL)	441.1	427	327.5	558	384	375.5	290	440.5	NS
ESR (mm/h)	33	36	18.5	45	19.8	12.5	7	22.5	< 0.05
CRP (mg/dL)	2.6	2.8	0.4	4.1	0.3	0.2	0	0.4	< 0.05

Q1: Lower quartile; Q3: Upper quartile; NS: Not significant.

Table 2 Characteristics of histological and endoscopic features in ulcerative colitis patients before and after induction therapy with infliximab

Parameter	Week 0	Week 8
Histopathological features		
Grade > 3	4/16	1/16
Grade 3	10/16	8/16
Grade 2	2/16	2/16
Grade 1	0/16	2/16
Grade 0	0/16	3/16
Irregular surface	12/16	6/16
Abnormal crypt architecture	9/16	8/16
Reduced number of the crypts	10/16	7/16
Cryptitis	11/16	6/16
Epithelial changes	8/16	6/16
Mucin depletion	6/16	6/16
Increased intraepithelial lymphocytes	3/16	5/16
Baron scale, mean ± SD	2.5 ± 0.6325	1.5 ± 0.9661 (P = 0.0033)
Baron 0	0/16	2/16
Baron 1	1/16	7/16
Baron 2	6/6	4/16
Baron 3	9/16	3/16

did not respond to cyclosporine therapy before IFX. All children received 5-ASA concomitantly with IFX; additionally, 10/16 participants (62.5%) were given steroids, and 13/16 (81.25%) thiopurines. Only one child (6.25%) received cyclosporine concomitantly with first IFX infusion. Four (25%) subjects had left-side UC (E2), eight (50%) extensive UC (E3), and four (25%) pancolitis (E4).

Clinical response

Clinical response, defined as a ⩾ 20-point reduction in PUCAI index, was observed in 14 of 16 (87.5%) patients. Clinical remission, defined as PUCAI index < 10 points, was achieved in 11/16 cases (68.75%). A significant decrease in the PUCAI score, ESR, and CRP concentration was observed after therapy. Moreover, a significant increase in body weight and hemoglobin concentration was documented when compared to baseline values (Table 1).

Mucosal healing

The mean Baron score at baseline (2.5) decreased significantly (P = 0.0033), down to 1.5, after IFX therapy. Mucosal healing (reduction in Baron scale) was observed in 11/16 (68.75%) patients. Endoscopic remission defined as 0 in Baron scale was achieved in two (12.5%) patients.

Histological remission defined as no inflammation (Geboes Index 0) was observed in three (18.75%) cases. General histological improvement, expressed by normal surface, crypt architecture, number of crypts, and lamina propria cellularity, was observed in six (37.5%) patients; another nine (56.25%) subjects did not show improvement, and aggravation was observed in one case (3.75%). The histological changes were not related to UC location. A reduction of the inflammatory process (reduction in Geboes Index score) was observed in 10 (62.5%) patients; no changes were documented in four (25%) cases, and in two (12.5%) individuals, inflammation was more severe. The exact histopathological characteristics of the patients and endoscopic grading system in the Baron scale are presented in Table 2.

Simultaneous clinical, endoscopic and histological improvement was observed in six (37.5%) patients. Of the specimens without acute inflammatory infiltrates in the epithelium (Geboes Index < 3) 5/9 (55.5%) had Baron score 0 or 1; of those with acute inflammation, 5/23 (21.7%) had a score of 1 or 2. A Baron score of 2 and 3 showed a better correlation with histology results [18/23 (78.2%) with Geboes Index ⩾ 3], but it was still statistically insignificant (Spearman's ρ, at week 0, P = 0.96, at week 8, P = 0.12). PUCAI index did not show any correlation with Baron score at week 0 and 8 (Spearman's ρ, at week 0, P = 0.96, at week 8, P = 0.51) PUCAI index and Geboes Index also showed no statistically significant correlation with Geboes Index (Spearman's ρ, at week 0, P = 0.77 at week 8, P = 0.79). Clinical, endoscopic and histological parameters for each patient at week 0 and 8 are presented in Table 3.

DISCUSSION

According to the American College of Gastroenterology guidelines from 2004, the goals of UC treatment should include inducing and maintaining the remission

Table 3 Correlation between clinical, endoscopic and histological parameters of disease activity

No.	Sex	Week 0			Week 8		
		PUCAI	Baron score	Geboes score	PUCAI	Baron score	Geboes score
1	M	70	3	> 3	15	3	3
2	F	75	2	3	25	1	3
3	M	50	2	3	< 10	1	0
4	F	50	3	3	< 10	1	3
5	M	55	2	> 3	< 10	2	3
6	F	25	3	2	< 10	3	3
7	M	40	3	> 3	0	0	2
8	M	10	2	3	65	1	> 3
9	M	45	3	3	0	2	1
10	F	45	3	3	< 10	2	2
11	F	85	3	2	< 10	0	0
12	F	60	3	3	< 10	2	3
13	F	30	2	3	< 10	1	0
14	M	25	2	3	< 10	1	3
15	F	50	3	> 3	35	3	3
16	F	70	1	3	30	1	1

M: Male; F: Female.

of symptoms and mucosal inflammation in order to improve quality of life. In 2010 the recommendation was modified, and reduction of the need for long-term corticosteroids and the minimization of cancer risk were added as therapeutic objectives[8]. Directing treatment paradigms to achieve those targets seems to be important, as reaching the goal may result in smaller numbers of complications, hospitalizations and surgical procedures[9,10]. A group of experts from the European Crohn's and Colitis Organization (ECCO) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) do not recommend routine endoscopic assessment in pediatric UC solely for assessing disease activity or response to treatment. Due to the lack of evidence that endoscopic confirmation of mucosal healing is significantly superior to clinical evaluation of remission, endoscopy is only recommended at diagnosis, before major treatment changes, when clinical assessment is the question, and for diagnosing complications (*e.g.,* stenosis and dysplasia) and super-infections[11]. Only the PUCAI score is advisable as a noninvasive primary outcome measure, both in clinical practice and in trials. In fact, histological healing is not recommended as a primary endpoint for therapeutic trials in adults or children with UC. However, a growing body of evidence suggests that the optimal target in UC therapy should be the complete regression of the inflammatory process, which is reached only when confirmed histologically[12]. Possibly, in new therapeutic approaches, achieving mucosal healing also from the histological point of view might add further value to future trials[13].

Importantly, there is no validated scoring system for the evaluation of disease activity. A histological assessment of inflammation in UC basically includes acute inflammatory cell infiltrates (polymorphonuclear cells in the lamina propria), crypt abscesses, mucin depletion, surface epithelial integrity, chronic inflammatory cell infiltrates (lympho-plasmocytes in the lamina propria), and crypt architectural irregularities[7]. In general, histological healing is either the absence of a residual mucosal inflammation with distinctive changes of crypt architectural distortion and/or atrophy, or entirely normal mucosa[14].

Since it is recommended to focus on the impact of drugs and biological therapies on mucosal healing, many studies addressed this problem, but mainly at the endoscopic level[15-19]. It is commonly known that the presence of mucosal healing from the endoscopic point of view does not necessarily indicate its presence at the microscopic level[20]. In our study, the results of mucosal healing assessed endoscopically after three infusions of IFX differed from those evaluated histologically: we obtained worse results on microscopic evaluation. Histological improvement, expressed by normal surface, crypt architecture, number of crypts, and lamina propria cellularity, was observed only in six (37.5%) patients, and no improvement was documented in most remaining cases (9/16, 56.25%). Furthermore, aggravation was observed in one patient (3.75%). Histological evaluation revealed no statistically significant changes in response to the induction *treatment.*

As far as histological healing is concerned, not many studies assessing the effect of drugs used in UC therapy are available. There have been many trials evaluating histological healing in adults treated with corticosteroids[21-24], salicylates[25-29] and immunomodulators[30,31], but only a few of them included adult patients with UC treated with a biological agent. Moreover, the problem in question has not been addressed in pediatric UC patients thus fur. In 2001, Bitton *et al*[32] were the first to report on clinical, biological and histological parameters that would predict time to clinical relapse. The basal plasmocytosis and rectal biopsy were the only factors that turned out to be significant predictors. Therefore, the authors concluded that these factors may help identify patients with inactive UC who require optimal maintenance therapy[32].

Hassan *et al*[33] studied the influence of IFX on histological changes. They investigated the immunohistological effect of infliximab in nine patients with moderate to severe UC. The patients received infliximab (5 mg/kg) at weeks 0, 2 and 6. Colonic biopsies were collected before therapy and at week 10. A scoring system that included polymorphonuclear infiltration of the epithelium and lamina propria, crypt abscesses, loss of glandular parallelism, crypt shortening and/or ramification, mucus epithelial depletion, involvement of muscularis mucosae and/or submucosa was used in this study. The total number of neutrophils, lymphocytes, and plasma cells in the lamina propria was counted in five high-power fields. At week 10, histological score

decreased significantly only in responders (67% of patients), and normal architecture was observed only in 33% of these subjects. Histological improvement was mainly manifested by virtual disappearance of neutrophils[33]. In our study, similar to the Hassan *et al*[33] trial, histological improvement, expressed by normal surface, crypt architecture, number of crypts, and lamina propria cellularity, was observed in 37.5% of patients. Moreover, a reduction of inflammatory process was observed in most patients (62.5%). Fratila *et al*[34] evaluated intracellular changes of the colonic mucosa in seven adult patients with UC refractory to standard treatment, before and 4 wk after initial infusion of IFX (5 mg/kg body weight)[34]. Severe alterations of the epithelium, such as microvilli depletion, shattering of epithelial junctions, cytoplasmic vacuolization, dilatation of the endoplasmic reticulum, pyknotic nuclei, and altered structure of mitochondria and Golgi complexes, were present before therapy. Rarefaction of the goblet cells with abnormal mucus formation and secretion was also noted. The chorion showed structural alteration of component cells, obstructed capillaries, erythrocyte extravasation and many plasmocytes and neutrophils. Improvement in morphology and function of the epithelial organelles, rich mucus secretion, and recovery of the chorionic components was observed after IFX therapy[34].

Correlation between clinical, endoscopy and histological assessment of disease activity has not been investigated thoroughly. Brahmania *et al*[35] examined the relationship between physician global assessment, laboratory blood tests (complete blood count, ferritin, CRP and albumin) and endoscopic findings in UC in adult patients to determine whether they could be adequate surrogates for endoscopy. After the analysis, they concluded that neither blood tests nor physician global assessment could replace endoscopy for assessing mucosal healing. However, *post hoc* analysis of data collected from 51 children with moderate-to-severe UC treated with IFX conducted by Turner *et al*[36] showed that PUCAI-defined remission had a high degree of concordance with complete mucosal healing (endoscopically assessed) at week 8 (33% of patients were in remission according to the PUCAI *vs* 31% with mucosal healing). In our study of patients with clinical remission (PUCAI < 10), endoscopically defined remission was noticed in 18.18% and histological defined remission in 27.27%. Among patients with clinical remission, histological parameters were distributed over almost all different grades: (Grade 3 - 45.45%; Grade 2 - 18.18%; Grade 1 - 9.09%; Grade 0 - 27.27%). Similar to the study conducted by Li *et al*[37], in our research, a relatively high percentage of patients (78.2%) with a Baron score of 2 and 3 had a Geboes Index $\geqslant$ 3 (correlation statistically insignificant). Furthermore, more than half of investigated patients with normal mucosa seen on endoscopy showed no inflammation on histology. Correlation between endoscopic and histological score assessment has been investigated by Lemmens *et al*[38]; 263 specimens from 131 patients with UC were scored using the Geboes and Riley histological scoring systems. Endoscopic scoring had been performed using the Mayo endoscopic subscore. Authors have noticed that both extremes of the histologic and endoscopic activity scores neatly correlate, but important misclassifications exist for mild disease.

Potential limitations of our study included the retrospective character of data analysis and the relatively small size of the sample. Only 16 of 23 consecutive UC pediatric patients treated with IFX were included in our analysis. The aim of this study was to analyze the influence of IFX induction therapy on mucosal healing at the microscopic level, and to compare the results with those assessed endoscopically. Histological remission was achieved only in 18.75% of investigated patients. Clinical remission, achieved by 68.75%, appears to be an unsatisfactory target for treatment of UC, since the disease could still be active at the histological level. These results provide the baseline for further analyses, especially the assessment of maintenance IFX therapy and the impact of mucosal healing on long-term remission and colectomy rate.

In conclusion, induction therapy with IFX had a positive influence on histological changes in 37.5% of UC patients. The treatment was effective in reducing intestinal inflammation (62.5% of the patients) and improving the clinical condition of children (87.5%). There was no significant correlation between Baron score, PUCAI index and Geboes Index. The impact of the histological healing after induction on the long-term clinical remission remains an area for further investigation.

COMMENTS

Background

Ulcerative colitis (UC) is a chronic idiopathic disease associated with inflammation in the gastrointestinal tract. Traditionally, the goal of the treatment is to reduce symptoms, mainly to induce and maintain clinical remission. In UC, in which lesions are usually limited to the mucosa, mucosal healing should be the ultimate therapeutic goal.

Research frontiers

The aim of this study was to assess mucosal healing in children with UC after infliximab (IFX) induction therapy, especially at the microscopic level. There are few studies focusing on this subject in adults with UC, but to the best of our knowledge, no data are available for pediatric patients. Furthermore, correlation between clinical, endoscopy and histological assessment of disease activity has not been investigated thoroughly.

Innovations and breakthroughs

In this study, the results of mucosal healing assessed endoscopically after three infusions of IFX differed from those evaluated histologically: the authors obtained worse results on microscopic evaluation. Histological improvement, expressed by normal surface, crypt architecture, number of crypts, and lamina propria cellularity, was observed only in six (37.5%) patients, and no improvement was documented in most remaining cases (9/16, 56.25%). Furthermore, aggravation was observed in one patient (3.75%). Clinical remission, achieved by 68.75%, appears to be an unsatisfactory target for treatment of UC, since the disease could still be active at the histological level.

The results showed no statistically significant correlation between Baron score, Pediatric Ulcerative Colitis Activity Index (PUCAI) index and Geboes Index.

Applications

The study results suggest that induction therapy with IFX has a positive influence on histological changes in more than one-third of UC patients. The treatment was effective in reducing intestinal inflammation (62.5% of patients) and improving the clinical condition of children (87.5%). These results provide the baseline for further analyses, especially assessment of maintenance IFX therapy and the impact of mucosal healing on long-term remission and colectomy rate in UC pediatric patients.

Peer-review

Despite the topic has been already extensively explored, the paper is well written and the design of the study is accurate and well detailed. The quality of the manuscript is good but it lacks novelty except for the fact that the study includes pediatric patient population.

REFERENCES

1 **Kornbluth A**, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004; **99**: 1371-1385 [PMID: 15233681 DOI: 10.1111/j.1572-0241.2004.40036.x]

2 **Colombel JF**, Rutgeerts P, Reinisch W, Esser D, Wang Y, Lang Y, Marano CW, Strauss R, Oddens BJ, Feagan BG, Hanauer SB, Lichtenstein GR, Present D, Sands BE, Sandborn WJ. Early mucosal healing with infliximab is associated with improved long-term clinical outcomes in ulcerative colitis. *Gastroenterology* 2011; **141**: 1194-1201 [PMID: 21723220 DOI: 10.1053/j.gastro.2011.06.054]

3 **Hanauer SB**. The role of biologics in ulcerative colitis. *Dig Dis* 2010; **28**: 497-500 [PMID: 20926878 DOI: 10.1159/000320408]

4 **Turner D**, Otley AR, Mack D, Hyams J, de Bruijne J, Uusoue K, Walters TD, Zachos M, Mamula P, Beaton DE, Steinhart AH, Griffiths AM. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. *Gastroenterology* 2007; **133**: 423-432 [PMID: 17681163 DOI: 10.1053/j.gastro.2007.05.029]

5 **Baron JH**, Connell AM, Lennard-Jones JE. Variation between observers in describing mucosal appearances in proctocolitis. *Br Med J* 1964; **1**: 89-92 [PMID: 14075156 DOI: 10.1136/bmj.1.5375.89]

6 **Levine A**, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, Fell J, Ruemmele FM, Walters T, Sherlock M, Dubinsky M, Hyams JS. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. *Inflamm Bowel Dis* 2011; **17**: 1314-1321 [PMID: 21560194 DOI: 10.1002/ibd.21493]

7 **Jenkins D**, Balsitis M, Gallivan S, Dixon MF, Gilmour HM, Shepherd NA, Theodossi A, Williams GT. Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. *J Clin Pathol* 1997; **50**: 93-105 [PMID: 9155688 DOI: 10.1136/jcp.50.2.93]

8 **Kornbluth A**, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010; **105**: 501-523; quiz 524 [PMID: 20068560 DOI: 10.1038/ajg.2009.727]

9 **Sandborn WJ**, Rutgeerts P, Feagan BG, Reinisch W, Olson A, Johanns J, Lu J, Horgan K, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009; **137**: 1250-160; quiz 1520 [PMID: 19596014 DOI: 10.1053/j.gastro.2009.06.061]

10 **Taylor KM**, Irving PM. Optimization of conventional therapy in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 646-656 [PMID: 21970871 DOI: 10.1038/nrgastro.2011.172]

11 **Turner D**, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, Dias JA, Bronsky J, Braegger CP, Cucchiara S, de Ridder L, Fagerberg UL, Hussey S, Hugot JP, Kolacek S, Kolho KL, Lionetti P, Paerregaard A, Potapov A, Rintala R, Serban DE, Staiano A, Sweeny B, Veerman G, Veres G, Wilson DC, Ruemmele FM. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. *J Pediatr Gastroenterol Nutr* 2012; **55**: 340-361 [PMID: 22773060 DOI: 10.1097/MPG.0b013e3182662233]

12 **Villanacci V**, Antonelli E, Geboes K, Casella G, Bassotti G. Histological healing in inflammatory bowel disease: a still unfulfilled promise. *World J Gastroenterol* 2013; **19**: 968-978 [PMID: 23467585 DOI: 10.3748/wjg.v19.i7.968]

13 **Vatn MH**. Mucosal healing: impact on the natural course or therapeutic strategies. *Dig Dis* 2009; **27**: 470-475 [PMID: 19897962 DOI: 10.1159/000233285]

14 **Levine TS**, Tzardi M, Mitchell S, Sowter C, Price AB. Diagnostic difficulty arising from rectal recovery in ulcerative colitis. *J Clin Pathol* 1996; **49**: 319-323 [PMID: 8655709 DOI: 10.1136/jcp.49.4.319]

15 **Kane S**, Lu F, Kornbluth A, Awais D, Higgins PD. Controversies in mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2009; **15**: 796-800 [PMID: 19213060 DOI: 10.1002/ibd.20875]

16 **Lichtenstein GR**, Rutgeerts P. Importance of mucosal healing in ulcerative colitis. *Inflamm Bowel Dis* 2010; **16**: 338-346 [PMID: 19637362 DOI: 10.1002/ibd.20997]

17 **Rutgeerts P**, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, Travers S, Rachmilewitz D, Hanauer SB, Lichtenstein GR, de Villiers WJ, Present D, Sands BE, Colombel JF. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462-2476 [PMID: 16339095]

18 **Rutgeerts P**, Vermeire S, Van Assche G. Mucosal healing in inflammatory bowel disease: impossible ideal or therapeutic target? *Gut* 2007; **56**: 453-455 [PMID: 17369375 DOI: 10.1136/gut.2005.088732]

19 **Hyams J**, Damaraju L, Blank M, Johanns J, Guzzo C, Winter HS, Kugathasan S, Cohen S, Markowitz J, Escher JC, Veereman-Wauters G, Crandall W, Baldassano R, Griffiths A. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2012; **10**: 391-9.e1 [PMID: 22155755 DOI: 10.1016/j.cgh.2011.11.026]

20 **Geboes K**, Dalle I. Influence of treatment on morphological features of mucosal inflammation. *Gut* 2002; **50** Suppl 3: III37-III42 [PMID: 11953331 DOI: 10.1136/gut.50.suppl_3.iii37]

21 **Gross V**, Bar-Meir S, Lavy A, Mickisch O, Tulassay Z, Pronai L, Kupcinskas L, Kiudelis G, Pokrotnieks J, Kovács A, Faszczyk M, Razbadauskas A, Margus B, Stolte M, Müller R, Greinwald R. Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis. *Aliment Pharmacol Ther* 2006; **23**: 303-312 [PMID: 16393311 DOI: 10.1111/j.1365-2036.2006.02743.x]

22 **Ruddell WS**, Dickinson RJ, Dixon MF, Axon AT. Treatment of distal ulcerative colitis (proctosigmoiditis) in relapse: comparison of hydrocortisone enemas and rectal hydrocortisone foam. *Gut* 1980; **21**: 885-889 [PMID: 7002739 DOI: 10.1136/gut.21.10.885]

23 **Sommers SC**, Korelitz BI. Mucosal-cell counts in ulcerative and granulomatous colitis. *Am J Clin Pathol* 1975; **63**: 359-365 [PMID: 234674]

24 **Truelove SC**, Hambling MH. Treatment of ulcerative colitis with local hydrocortisone hemisuccinate sodium; a report on a controlled therapeutic trial. *Br Med J* 1958; **2**: 1072-1077 [PMID: 13584853]

25 **Green JR**, Mansfield JC, Gibson JA, Kerr GD, Thornton PC. A double-blind comparison of balsalazide, 6.75 g daily, and sulfasalazine, 3 g daily, in patients with newly diagnosed or relapsed active ulcerative colitis. *Aliment Pharmacol Ther* 2002; **16**: 61-68 [PMID: 11856079 DOI: 10.1046/j.1365-2036.2002.01150.x]

26 **Kruis W**, Kiudelis G, Rácz I, Gorelov IA, Pokrotnieks J, Horynski M, Batovsky M, Kykal J, Boehm S, Greinwald R, Mueller R. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. *Gut* 2009; **58**: 233-240 [PMID: 18832520 DOI: 10.1136/gut.2008.154302]

27 **Malchow H**, Gertz B. A new mesalazine foam enema (Claversal

Foam) compared with a standard liquid enema in patients with active distal ulcerative colitis. *Aliment Pharmacol Ther* 2002; **16**: 415-423 [PMID: 11876694 DOI: 10.1046/j.1365-2036.2002.01199.x]

28 **Mansfield JC**, Giaffer MH, Cann PA, McKenna D, Thornton PC, Holdsworth CD. A double-blind comparison of balsalazide, 6.75 g, and sulfasalazine, 3 g, as sole therapy in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2002; **16**: 69-77 [PMID: 11856080 DOI: 10.1046/j.1365-2036.2002.01151.x]

29 **Rao SS**, Dundas SA, Holdsworth CD, Cann PA, Palmer KR, Corbett CL. Olsalazine or sulphasalazine in first attacks of ulcerative colitis? A double blind study. *Gut* 1989; **30**: 675-679 [PMID: 2567266]

30 **D'Haens G**, Lemmens L, Geboes K, Vandeputte L, Van Acker F, Mortelmans L, Peeters M, Vermeire S, Penninckx F, Nevens F, Hiele M, Rutgeerts P. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001; **120**: 1323-1329 [PMID: 11313301 DOI: 10.1053/gast.2001.23983]

31 **Paoluzi OA**, Pica R, Marcheggiano A, Crispino P, Iacopini F, Iannoni C, Rivera M, Paoluzi P. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. *Aliment Pharmacol Ther* 2002; **16**: 1751-1759 [PMID: 12269968 DOI: 10.1046/j.1365-2036.2002.01340.x]

32 **Bitton A**, Peppercorn MA, Antonioli DA, Niles JL, Shah S, Bousvaros A, Ransil B, Wild G, Cohen A, Edwardes MD, Stevens AC. Clinical, biological, and histologic parameters as predictors of relapse in ulcerative colitis. *Gastroenterology* 2001; **120**: 13-20 [PMID: 11208709 DOI: 10.1053/gast.2001.20912]

33 **Hassan C**, Ierardi E, Burattini O, De Francesco V, Zullo A, Stoppino G, Panella C, Morini S. Tumour necrosis factor alpha down-regulation parallels inflammatory regression in ulcerative colitis patients treated with infliximab. *Dig Liver Dis* 2007; **39**: 811-817 [PMID: 17652038 DOI: 10.1016/j.dld.2007.06.003]

34 **Fratila OC**, Craciun C. Ultrastructural evidence of mucosal healing after infliximab in patients with ulcerative colitis. *J Gastrointestin Liver Dis* 2010; **19**: 147-153 [PMID: 20593047]

35 **Brahmania M**, Bernstein CN. Physician global assessments or blood tests do not predict mucosal healing in ulcerative colitis. *Can J Gastroenterol Hepatol* 2014; **28**: 325-329 [PMID: 24945187]

36 **Turner D**, Griffiths AM, Veerman G, Johanns J, Damaraju L, Blank M, Hyams J. Endoscopic and clinical variables that predict sustained remission in children with ulcerative colitis treated with infliximab. *Clin Gastroenterol Hepatol* 2013; **11**: 1460-1465 [PMID: 23672831 DOI: 10.1016/j.cgh.2013.04.049]

37 **Li CQ**, Xie XJ, Yu T, Gu XM, Zuo XL, Zhou CJ, Huang WQ, Chen H, Li YQ. Classification of inflammation activity in ulcerative colitis by confocal laser endomicroscopy. *Am J Gastroenterol* 2010; **105**: 1391-1396 [PMID: 19935787 DOI: 10.1038/ajg.2009.664]

38 **Lemmens B**, Arijs I, Van Assche G, Sagaert X, Geboes K, Ferrante M, Rutgeerts P, Vermeire S, De Hertogh G. Correlation between the endoscopic and histologic score in assessing the activity of ulcerative colitis. *Inflamm Bowel Dis* 2013; **19**: 1194-1201 [PMID: 23518809 DOI: 10.1097/MIB.0b013e318280e75f]

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