How Has the Disease Course of Pediatric Ulcerative Colitis Changed Throughout the Biologics Era? A Comparison with the IBSEN Study

Dear Editor-in-Chief

We thank the editor and the reviewers for their comments. We added some contents and edited manuscript as reviewers and editors suggested. The manuscript is also edited by another native English-speaking expert.

● Comments of Science editor

In this study，the authors compare the clinical course of ulcerative colitis before and after the introduction of biological agents. It is an interesting story and the paper is well written. However, there are some comments need to be taken into consideration. Some details need to be described like IBSEN study, endoscopic procedure and so on. The figures and tables need to be well organized. And other questions asked by reviewers. The references need to be updated according to the requirements of this journal. There are too few references within 5 years.

→ Response

Thank you for your comment. We described more about IBSEN study in introduction section (page 5, 2nd paragraph) and we changed some references within 5 years (reference #3, #27, #34, #35, #37, #39). We also answered reviewer's questions in next pages.

● Comments of company editor-in-chief

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines

are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

→ Response

Thank you for your comment. We organized the figures and tables as you recommended. We attached revised figure and table files in F6Publishing system.

● Comments of reviewer #1

In this article, the authors describe the IFX-effect on the Korean pediatric cohorts with ulcerative colitis. It is an interesting study. It may be worth publishing. However, there are some concerns before publishing the article.

Q1. The authors describe the comparison of the IBSEN study. However, the details of the IBSEM study have not been well described in the sentences.

→ Response

Thank you for your comment. As you suggested, we described more details about IBSEN study in introduction section (page 5, 2nd paragraph). We attached the paragraph below. Highlighted sentences are newly added sentences.

The age of onset of UC can be anywhere from 15 to 30 or over 60, and the incidence of UC is lower than that of Crohn's disease in children [5]. For this reason, an insufficient number of large-scale studies and long-term follow-up studies have been done in pediatric patients with UC, and more work must be done to evaluate the clinical course of UC in such patients. The IBSEN study evaluated the long-term clinical course and outcomes of 423 adult patients with UC during the first 10 years. Mortality risk and cumulative colorectal resection were evaluated as clinical outcomes. The proportion of patients who have relapsed and the proportion of patients who remain in remission were evaluated as a clinical course. In addition, the authors divide the disease course of UC into 4 types and show them in graphs, and these graphs became a representative figure of this paper [6]. However, this study was done before any biological agents were approved as treatments. No studies have compared the clinical course of UC before and after the introduction of biological agents in a single cohort.

Q2. The endoscopic procedure has not been described. Any AEs during the procedure?

→ Response

Thank you for your comment. As you suggested, we described endoscopic procedure (Page 7, 2nd paragraph). We attached the paragraph below. There was no any AEs during the procedure. Let us know If you think it is necessary to write about AE in the manuscript.

Colonoscopy was performed at the time of initial diagnosis and at intervals of 1 to 2 years during the follow-up period. The colonoscopy was performed with CF scope after sedation with midazolam and pethidine. All procedure reached to the cecum and examined the entire colon. As endoscopic findings, the characteristic findings of ulcerative colitis such as peri-appendiceal patches, demarcation line, mucosal edema, decreased vascularity of loss of vascularity, and superficial tiny ulcers with continuity were observed and described. We reviewed the colonoscopy findings at 2 and 5 years after the start of treatment. Remission was defined as endoscopic mucosal healing, which means that no lesion was observed and the MES was 0 with histological healing (Geboes grade 0-1). The reason for excluding MES 1 is that the authors aimed at deep remission because they experienced cases of MES 1 that relapsed easily. In addition, we investigated the drugs received by both groups of patients during the follow-up period.

Q3. The definition of remission is critical in this study. Would you explain the reason for excluding MES1 as a remission? If so, did you take biopsy samples? Did they achieve histological healing (= Geboes grade 0–1)?

→ Response

Thank you for your comment. Since our 20 years of treatment experience has shown that relapses can occur even with MES 1, thereby we strictly target MES 0 for remission. In addition, since the number of patients who actually reached MES 0 is certain, only MES 0 was evaluated as a remission state for these reasons. All of them achieved histological healing (= Geboes grade 0–1). In order not to confuse the readers about these contents, it has been added to the manuscript as well (Page 7, 2nd paragraph, which is same paragraph with question 2).

Q4. Fig4 has too many graphics that are confusing for readers. Please reconstruct each figure according to before and after the approval of IFX treatment.

→ Response

Thank you for your comment. As you suggested, we briefly modified the graphs. We uploaded new figure in F6Publishing system.

● Comments of reviewer #2

In this paper, the authors compare the clinical course of UC before and after the introduction of biological agents, and concluded that the incidence of relapse has decreased and the steroid-free period has increased after the introduction of the biological agent. This paper is well written and the results are clinically interesting. I only suggest the followings items which might strengthen the work.

Q1. If possible, please show the proportions of steroid-dependent and steroid-refractory patients in both Group A and Group B in Table1.

→ Response

Thank you for your comment. As you suggested, we added the proportions of steroid-dependent and steroid-refractory patients in both Group A and Group B in Table1. The contents were also added to the manuscript (page 9, last paragraph). We also attached the new table and the paragraph below.

Within 3 months of diagnosis, most patients in both groups were treated with 5-aminosalicylate and immunosuppressants, primarily azathioprine. In both groups, about 50% of patients used corticosteroids to reduce disease activity at the time of diagnosis. Of the 21 patients who used corticosteroids in group A, 8 (48.1%) showed dependence and 1 (4.8%) showed refractory findings. In group B, 9/30 (30.0%) of patients were corticosteroid-dependent and 1/30 (3.3%) were corticosteroid-refractory. There was no statistical difference between the two groups.

Table 1. Demographic and clinical features of the two groups before and after infliximab approval

	Group A (N = 48)	Group B (N = 62)	*P* value
Age at diagnosis, years	14.4 (12.2-17.1)	15.8 (13.1-16.5)	0.574[c]
Total duration of follow up with treatment, years	4.0 (4.0-5.0)	5.5 (3.0-6.9)	0.073[c]
PUCAI[a] at diagnosis	35 (30-65)	45 (35-55)	0.969[c]
Hemoglobin at diagnosis, g/dl	12.3 (10.5-14.1)	12.1 (9.6-13.5)	0.245[c]
Albumin at diagnosis, g/dl	4.3 (4.0-4.6)	4.2 (3.9-4.6)	0.702[c]
ESR at diagnosis, mm/hr	14.5 (7-31.3)	20 (7.5-39)	0.249[c]
CRP at diagnosis, mg/dl	0.04 (0.03-0.13)	0.12 (0.03-0.56)	0.791[c]
Disease extent of Paris classification at diagnosis			0.018[d]
E1 Proctitis	18 (37.5)	13 (21)	
E2 Left colitis	8 (16.7)	8 (12.9)	
E3 Right colitis	6 (12.5)	7 (11.3)	
E4 Pancolitis	16 (33.3)	34 (54.8)	
Mayo endoscopic subscore at diagnosis[b]			0.310[d]
0 Normal or inactive	0	0	
1 Mild	12 (25.0)	7 (11.3)	
2 Moderate	26 (54.2)	43 (69.4)	
3 Severe	10 (20.8)	12 (19.4)	
Corticosteroid use at baseline	21 (43.8)	30 (48.4)	0.630[d]
Corticosteroid-dependent	8/21 (48.1)	9/30 (30.0)	0.550 [d]
Corticosteroid-refractory	1/21 (4.8)	1/30 (3.3)	0.360 [d]
Cumulative number receiving medication by 3 months after diagnosis			
5-Aminosalicylate	48 (100)	60 (96.8)	0.211[d]
Azathioprine	42 (87.5)	51 (82.3)	0.453[d]
Methotrexate	0 (0)	1 (1.6)	
Cyclosporine	1 (2.1)	0 (0)	

Values are n (percentage) or median (interquartile range); N, number of patients

[a] Pediatric Ulcerative Colitis Activity Index (PUCAI) is a 6-item disease activity index intended for use in pediatric UC clinical trials with a score ranging from 0 – 85.

[b] Mayo endoscopy subscores were as follows: 0, normal or inactive disease; 1, mild disease; 2, moderate disease; and 3, severe disease.

[c] χ^2 test

[d] Mann-Whitney test

Q2. Please show the percentages of patients taking biologics other than infliximab in Group B after 2 and 5 years of treatment.

→ Response

Thank you for your comment. As you suggested, we added information of medication and biological agents in table 2. Let us know if you want only information of biologics in the table 2. We also attached the new table below.

Table 2. Comparison of composition of drugs for treatment and disease states according to colonoscopy findings 2 and 5 years after diagnosis before (group A) and after (group B) infliximab approval.

	Group A (N = 48)	Group B (N = 62)	*P* value
Maintenance treatment 2 year after diagnosis			
None	0	5 (8.1)	0.045
5-Aminosalicylate	47 (97.9)	46 (74.2)	0.001
Azathioprine	43 (89.6)	36 (58.1)	0.001
Infliximab	0	34 (54.8)	<0.001
Adalimumab	0	0	
Vedolizumab	0	0	
Ustekinumab	0	0	
Tofacitinib	0	0	
Disease extent of Paris classification 2 years after diagnosis			0.012 [b]
Remission	14 (29.2)	31 (50.0)	
E1 Proctitis	13 (27.1)	11 (17.7)	
E2 Left colitis	2 (4.2)	8 (12.9)	
E3 Right colitis	6 (12.5)	8 (12.9)	
E4 Pancolitis	13 (27.1)	4 (6.5)	
Mayo endoscopic subscore 2 years after diagnosis[a]			0.037 [b]
0 Normal or inactive	15 (24.2)	33 (53.2)	
1 Mild	24 (50.0)	21 (33.9)	
2 Moderate	8 (16.7)	8 (12.9)	
3 Severe	1 (2.1)	0	
	Group A (N = 24)	**Group B (N = 31)**	***P* value**
Maintenance treatment 5 year after diagnosis			
None	2 (8.3)	5 (16.1)	0.394
5-Aminosalicylate	21 (87.5)	15 (48.4)	0.003
Azathioprine	14 (58.3)	14 (45.2)	0.337
Infliximab	0	18 (58.1)	<0.001
Adalimumab	0	2 (6.5)	
Vedolizumab	0	1 (3.2)	
Ustekinumab	0	0	
Tofacitinib	0	0	
Disease extent of Paris classification 5 years after diagnosis			0.016 [b]
Remission	3 (12.5)	13 (41.9)	
E1 Proctitis	9 (37.5)	9 (29.0)	
E2 Left colitis	3 (12.5)	4 (12.9)	
E3 Right colitis	2 (8.3)	2 (6.5)	
E4 Pancolitis	7 (29.2)	3 (9.7)	
Mayo endoscopic subscore 5 years after diagnosis[a]			<0.001 [b]
0 Normal or inactive	3 (12.5)	13 (41.9)	
1 Mild	6 (25.0)	16 (51.6)	
2 Moderate	14 (58.3)	2 (6.5)	
3 Severe	1 (4.2)	0	

Values are n (percentage).

[a] Mayo endoscopy subscores were as follows: 0, normal or inactive disease; 1, mild disease; 2, moderate disease; and 3, severe disease.

[b] Mann-Whitney test