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ORIGINAL ARTICLE

The efficacy of infliximab combined with surgical treatment of fistulizing perianal Crohn's disease: Comparative analysis according to fistula subtypes

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KEYWORDS
Crohn's disease;
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Summary *Background/Objective:* Infliximab is regarded as an effective therapeutic to treat Crohn's disease. This study aimed to assess the efficacy of infliximab combined with surgery and to analyze clinical manifestations according to fistula subtypes in patients with fistulizing perianal Crohn's disease.
Methods: From April 2013 to December 2015, 47 patients with perianal Crohn's disease in two hospitals of South Korea (Goo Hospital, Gangnam Severance Hospital) were evaluated retrospectively. Patients were categorized into two groups as simple fistula (n = 20) and complex fistula group (n = 27). All patients received 5 mg/kg of infliximab intravenously at 0, 2, and 6 weeks after surgical treatments. Then every eight weeks, the responders continued to receive 5 mg/kg infliximab for maintenance therapy.
Results: Complete response of induction therapy was 72.3%, and partial response was 27.7%. After maintenance therapy, complete response was 97.9% and partial response was 2.1%. There was no patient without a response to infliximab in this study. The median time to the

Abbreviations: TNF-α, Tumor necrosis factor α; CDAI, Crohn's disease activity index; PDAI, Perianal Crohn's disease activity index; BMI, Body mass index; 5-ASA, Aminosalicylates; IQR, Interquartile range.

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first fistula closure was 6.00 ± 8.00 weeks. Infliximab was used on average 2.13 ± 0.71 times until the first fistula closure. The rate of recurrence was 8.5% and adverse events were 4.2%. In comparison with clinical manifestations between simple and complex fistula groups, there was no significant difference except for the coexistence of perianal abscess.
Conclusions: Combined surgical and infliximab therapy was efficacious to treat fistulizing perianal Crohn's disease with rapid treatment response and favorable clinical outcomes. It is expected that this top-down strategy with combining surgeries can overcome previous limitations in treating perianal Crohn's disease.

1. Introduction

Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract, which features transmural inflammation predisposing it to fistula formation.[1] Although the cause of Crohn's disease is unclear, fistula formation of Crohn's disease occurs in approximately 17%–50% of patients.[2,3] Especially, perianal fistulas are common manifestations of Crohn's disease with an incidence of 21%–40%.[4–6] Because they tend to increase morbidities as well as to decrease quality of life, various approaches to treat fistulizing perianal Crohn's disease were developed.

Among the therapeutics for Crohn's disease, infliximab, a chimeric monoclonal antibody for tumor necrosis factor α (TNF-α), is regarded as an effective agent to treat fistulizing Crohn's disease. Because it binds to precursors of TNF-α and neutralize the pro-inflammatory responses, there were expectations that infliximab can reduce inflammatory activities and improve healing rates in patients with Crohn's disease. Present et al. reported that the rate of complete response for fistula closure was 46% of the infliximab group, which was higher than 13% of the placebo group ($P = 0.001$).[7] In addition, the ACCENT-II trial demonstrated that the use of infliximab for maintenance therapy was effective and safe to treat patients with fistulizing Crohn's disease.[3] At the 54th week, complete response of the infliximab maintenance group was 36%, as compared with 19% of the placebo group ($P = 0.009$).

In the development of a top-down therapy, infliximab is considerable as an initial treatment for moderate-to-severe Crohn's disease prior to other therapeutics. Especially, combined surgical and infliximab therapy showed improved healing rates and reduced recurrent rates in the complex fistulas.[8–10] However, because perianal fistulas are categorized by various subtypes depending on their locations and fistula openings, the assessment for treatment response of infliximab is required in accordance with fistula subtypes. In addition, the phenotypes and clinical characteristics tend to be different between Eastern and Western countries. Although the response of the anti-TNF agents in Asia is expected to be higher than the Western countries, there is a lack of published reports on the efficacy of infliximab for perianal Crohn's disease.[11] In these regards, this study aims to evaluate the efficacy of infliximab combined with surgical procedures in patients with fistulizing perianal Crohn's disease in Korea and to analyze the treatment response according to fistula subtypes.

2. Methods

2.1. Study population and data collection

From April 2013 to December 2015, patients diagnosed with perianal Crohn's disease in two hospitals of South Korea (Goo Hospital and Gangnam Severance Hospital) were reviewed retrospectively. Among them, patients who underwent combined surgical and infliximab treatment were evaluated in this study. Patients who used concomitant therapeutic agents related with Crohn's disease were also included. However, patients who had Crohn's disease without perianal involvement, colorectal malignancy, active tuberculosis, or severe infection were excluded.

Before surgery, all patients were assessed by clinical examination, colonoscopy, computed tomography, anorectal endoscopic ultrasound and pelvic magnetic resonance imaging to evaluate pathologic lesions and to determine the types of fistula-in-ano. Perianal fistulas were classified by intraoperative procedures following Park's classification: superficial, intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric fistula.[12] Crohn's disease activity index (CDAI) and perianal Crohn's disease activity index (PDAI) were evaluated to assess the severity of Crohn's disease. The quantiferon test, which is used to diagnose tuberculosis, was performed before using infliximab to prevent the recurrence of tuberculosis.

Surgical treatments were performed by seton drainage, fistulotomy, or fistulectomy including incision and drainage. Fistulotomy was preferred for the low type of fistula without proctitis. However, seton procedure or fistulectomy were preferred in fistulas with perianal abscess in complex fistulas. These surgical procedures were determined by the locations and subtypes of fistulas during the operation.

After surgery, infliximab was used within postoperative 1 week following the protocol. All patients received infliximab on schedule. This study was approved by the Institutional Review Boards (IRB No. 3-2016-0092).

2.2. Evaluation parameters

The patients were categorized into two types as simple fistula group and complex fistula group. According to Park's classification, patients who had superficial or

intersphincteric fistula were classified as the simple fistula group. On the other hand, patients who had transsphincteric, suprasphincteric, or extrasphincteric fistulas were determined as the complex fistula group (Fig. 1).

All patients were evaluated for combined morbidities, familial or smoking histories, concomitant medications, and previous history of perianal surgery before using infliximab. Rectal inflammation was assessed by performing a preoperative colonoscopy. Luminal Crohn's disease, which involves the gastrointestinal tract was evaluated by preoperative imaging studies and colonoscopy.

The period of Crohn's disease was calculated by the duration from the first diagnosis to the last follow-up. The duration of perianal disease was defined as the time from receiving the first perianal surgery to the last follow-up. The existence of concomitant perianal abscess was the condition that patients had a perianal fistula with perianal abscess simultaneously. Time to the first fistula closure was calculated by the period from the first use of infliximab to the fistula closure. Both CDAI and PDAI were evaluated before the initial and after the last infusion of infliximab during the follow-up period. Recurrence was defined when there was a newly developed fistula in patients with complete or partial response to infliximab. Duration of recurrence was calculated by the time between the first fistula closure and recurrence.

2.3. Definition of treatment response

Treatment response was assessed every visit by clinical symptoms, physical examination, and imaging studies. It was classified as complete, partial and no response. Complete response was defined as complete closure of fistula openings without any drainage. Partial response was defined as reduction of fistula size more than 50 percent from the baseline including numbers of fistula drainage. All other clinical results were categorized as no response. The outcomes of induction therapy were assessed at 10—14 weeks and treatment response of maintenance therapy was evaluated every 8 weeks.

2.4. Treatment protocol

After surgical treatment of perianal Crohn's disease, all patients received induction therapy, in which infliximab at a dose of 5 mg/kg of body weight is given intravenously at the intervals of 0, 2, and 6 weeks. Then, the responders of induction therapy continued to receive infliximab 5 mg/kg every eight weeks for maintenance therapy. If the patients had complete response, the use of infliximab was stopped and changed to azathioprine. In addition, patients who had partial response continued the maintenance therapy and assess the treatment response every visit. On the other hand, patients who had no response discontinued infliximab.

All surgical procedures were performed before the use of infliximab. All patients received antibiotics before surgery. After the surgery, seton was removed when the fistulas closed completely. Adverse events related with infliximab were reported in the electronic charts. Patients with adverse events discontinued infliximab and altered the therapeutic agents.

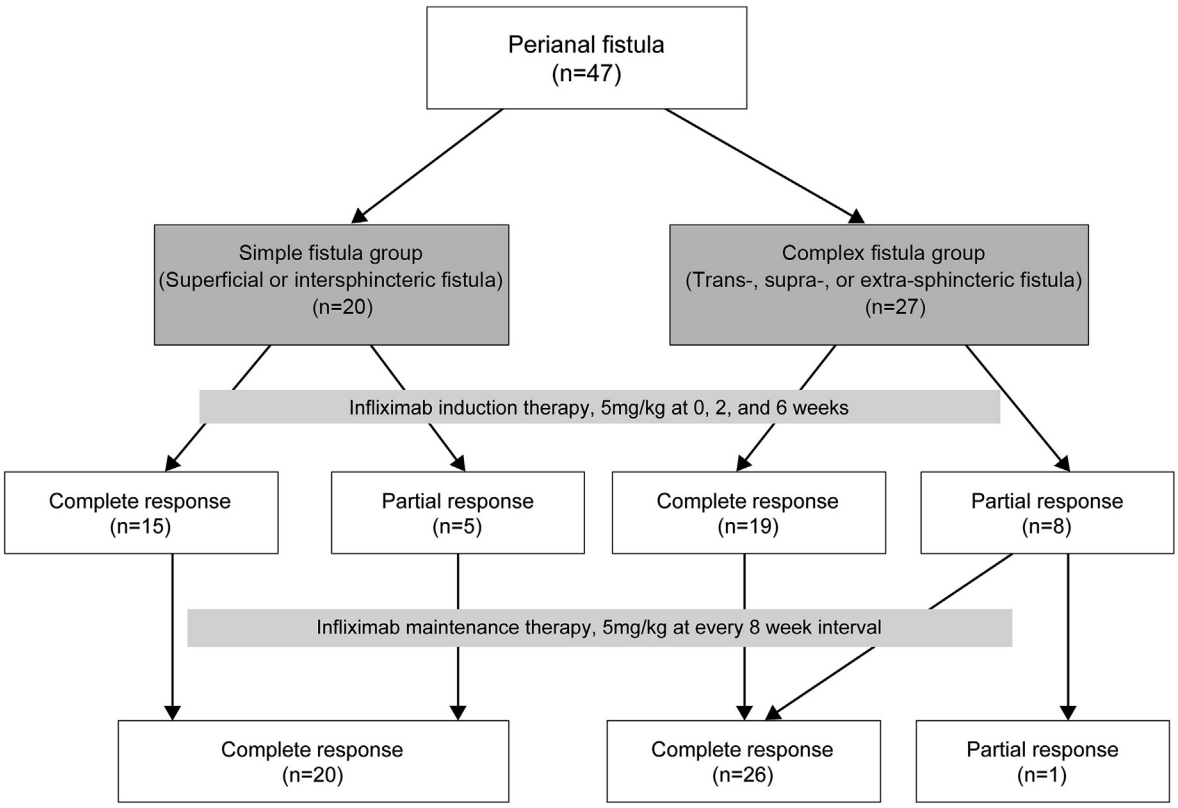

Figure 1 Study scheme and treatment response classified by Park's classification.

2.5. Statistical analysis

All statistical data were analyzed using the SPSS program (Statistical Product and Service Solution 20 for Windows; SPSS Inc., Chicago, IL), and SAS version 9.2 (SAS Institute, Cary, NC, USA). Continuous variables were calculated using the independent *t*-test or Mann–Whitney test. The comparison of PDAI before and after use of infliximab was analyzed by the paired t-test. Categorical variables were assessed by the chi-square test or Fisher's exact test. A P value less than 0.05 was considered statistically significant in this study.

3. Results

3.1. Patient characteristics

Among a total of 47 patients, the number of males were higher than the females (72.3% vs. 27.7%). Patients under 30 years old were 85.1%: teenagers (34.0%) and twenties (51.1%). The average value of body mass index (BMI) was 20.8 ± 3.2 kg/m^2 (mean ± SD). There were 6.3% of patients with co-morbidities, and 8.5% with familial history of Crohn's disease. In addition, 25.5% of patients had previous smoking history. The average Crohn's disease period was 2.0 ± 2.6 years and perianal disease was 2.1 ± 2.0 years. There were 72.3% of patients with rectal inflammation and 48.9% with luminal Crohn's disease, which involved the ileum, colon and rectum simultaneously. Patients who underwent previous perianal surgeries were 82.9%. Seton drainage was the most common previous surgical procedures (38.3%) among them. 5-aminosalicylates (5-ASA) was used in 91.5% of patients for Crohn's medication prior to using infliximab. There were 2.1% of patients who previously used biologics (Table 1).

Table 1 Patient characteristics.

Variables	n = 47
Sex (n, %)	
Male	34 (72.3%)
Female	13 (27.7%)
Age (year)	23.5 ± 8.1 (range, 13–48)
10–19 years	16 (34.0%)
20–29 years	24 (51.1%)
30–39 years	3 (6.4%)
≥ 40 years	4 (8.5%)
BMI (kg/m^2)	20.8 ± 3.2 (15.2–28.7)
Co-morbidity	3 (6.3%)
Gallbladder stone	1 (2.1%)
Ureteral stone	1 (2.1%)
Old pulmonary tuberculosis	1 (2.1%)
Familial history of Crohn's disease	4 (8.5%)
Smoking history	12 (25.5%)
Duration of Crohn's disease (year)	2.0 ± 2.6 (0–11)
Duration of perianal disease (year)	2.1 ± 2.0 (0–8)
Rectal inflammation	34 (72.3%)
Involved GI areas	
Ileum (or rectum only)	9 (19.2%)
Ileum + colon (or rectum)	15 (31.9%)
Ileum + colon + rectum	23 (48.9%)
Previous perianal surgery prior to IFX	
None	9 (19.1%)
1 time	15 (31.9%)
2 times	15 (31.9%)
≥3 times	8 (17.1%)
History of previous perianal surgery	
None	10 (21.2%)
Fistulotomy	8 (17.0%)
Seton procedure	18 (38.3%)
Fissurectomy	4 (8.5%)
Incision and drainage	3 (6.4%)
Seton ± fistulotomy (or fissurectomy)	4 (8.5%)
Previous medications prior to IFX	
5-ASA	24 (51.1%)
5-ASA and AZP	10 (21.3%)
5-ASA, AZP, and steroid	1 (2.1%)
5-ASA and steroid	4 (8.5%)
5-ASA and antibiotics	4 (8.5%)
Antibiotics only	3 (6.4%)
Biologics	1 (2.1%)
Preoperative ESR level	18.6 ± 12.8 (2.0–49.0)
Preoperative CRP level	3.9 ± 6.6 (0.1–44.6)

BMI, body mass index; IFX, infliximab; ASA, aminosalicylate; AZP, azathioprine.

3.2. Clinical manifestations and concomitant treatments with infliximab

Transsphincteric type was the most common perianal fistula with 44.7%, and intersphincteric type was the second most common with 42.6% among the patients. On the other hand, there were 10.6% of patients with the extrasphincteric type and 2.1% with the suprasphincteric type. Patients had two or more fistulas were 57.5%. Perianal abscess was combined concomitantly in 80.9% and rectovaginal fistula was developed in 4.3% of patients. The most common concomitant surgical procedure was seton drainage (72.3%) in this study. Fistulotomy and fistulectomy were performed in the 10.6% and 4.3% of patients, respectively. Patients who used 5-ASA concomitantly combined with both surgical procedures and infliximab were 80.9% (Table 2).

3.3. Treatment response after combined surgical and infliximab therapy

The median follow-up period was 11.0 ± 8.0 months (interquartile range (IQR), 7.0–15.0). The average time to the first fistula closure was 7.64 ± 4.81 weeks (range, 2–23) and the median time was 6.00 ± 8.00 weeks (IQR, 5–13). As shown in Fig. 2, most patients in both the simple and complex fistula groups had a first fistula closure within 6 weeks. Infliximab was used an average of 2.13 ± 0.71 times to the first fistula closure. 55.3% of the patients had the first fistula closure at the second use of infliximab, and 25.5% of

Table 2 Clinical manifestations and concomitant treatments with infliximab.

Variables	n = 47
Subtypes of perianal fistulas (n, %)	
Intersphincteric	20 (42.6%)
Transsphincteric	21 (44.7%)
Suprasphincteric	1 (2.1%)
Extrasphincteric	5 (10.6%)
Number of fistulas (n,%)	
1	20 (42.5%)
2	14 (29.8%)
≥3	13 (27.7%)
Concomitant perianal abscess	38 (80.9%)
Rectovaginal fistula	2 (4.3%)
Concomitant surgical treatment with IFX	
Seton procedure	34 (72.3%)
Fistulotomy	5 (10.6%)
Fistulectomy	4 (8.5%)
Incision and drainage	2 (4.3%)
Seton + coring out fistulectomy	2 (4.3%)
Concomitant medications with IFX	
5-ASA	38 (80.9%)
5-ASA + AZP	5 (10.6%)
5-ASA + steroid	2 (4.3%)
5-ASA + AZP + steroid	1 (2.1%)
Only antibiotics	1 (2.1%)

IFX, infliximab; ASA, aminosalicylate; AZP, azathioprine.

the patients had it at the third time of infliximab use. The total numbers to use infliximab until the first fistula closure was 7.96 ± 2.47 times.

After induction therapy, the rate of complete response was 72.3%, and partial response was 27.7%. After maintenance therapy, complete response was 97.9% and partial response was 2.1%. There was no patient without a response to infliximab in this study.

Both CDAI and PDAI values after infliximab therapy were lower than before infliximab use. The average CDAI was 208.5 ± 66.5 before infliximab uses compared with 98.2 ± 26.6 after infliximab uses. The average difference of PDAI between the before and after infliximab uses was 9.1.

Recurrence of perianal fistula occurred in four patients (8.5%) and the average time to recurrence was 4.75 ± 2.06 months. The discontinuation of infliximab occurred in one patient because of psoriasiform dermatitis during maintenance therapy. There were two adverse events: perianal bleeding and skin eruption (Table 3).

3.4. Subanalysis of the response according to fistula subtypes

As shown in Fig. 1, all patients were categorized as either the simple or complex fistula group: 20 patients in the simple fistula group and 27 patients in the complex fistula group. After induction therapy, 15 patients had complete response and 5 patients had partial response in the simple fistula group. On the other hand, there were 19 patients with complete response and 8 patients with partial response in the complex fistula group. All patients in simple fistula group had complete response after maintenance therapy. However, patients in the complex fistula group had complete response except for one patient with a partial response.

According to the treatment response categorized by Park's classification, patients with intersphincteric, transsphincteric or suprasphincteric fistulas accomplished complete response in all patients for maintenance therapy (Fig. 3). However, patients with extrasphinteric fistulas had 40% of complete response in the induction therapy and 80% of complete response in the maintenance therapy.

The average time to the first fistula closure was not significantly different between the simple and complex fistula groups. Infliximab uses of the complex fistula group were larger than the simple fistula group with marginally significance (2.30 ± 0.61 vs. 1.90 ± 0.79, P = 0.077). Treatment responses in both induction and maintenance therapy were not significantly different between the simple

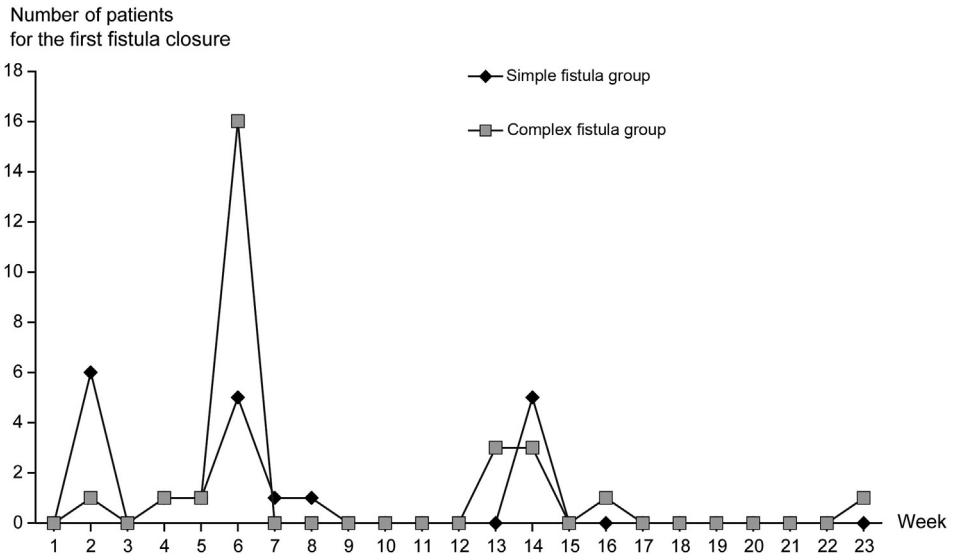

Figure 2 Time to the first fistula closure.

Table 3 Treatment response after combined surgeries with infliximab.

Variables	n = 47
Time to the first fistula closure (week)	
Mean ± SD (range)	7.64 ± 4.81 (2–23)
Median ± IQR (Q1-Q3)	6.00 ± 8.00 (5–13)
Average uses of IFX to the first fistula closure	2.13 ± 0.71 (1–4)
Detailed uses of IFX to the first fistula closure	
1st time	8 (17.0%)
2nd time	26 (55.3%)
3rd time	12 (25.5%)
4th time	1 (2.1%)
Total uses of IFX	7.96 ± 2.47 (3–12)
Response to IFX at induction therapy	
Complete response	34 (72.3%)
Partial response	13 (27.7%)
No response	0 (0.0%)
Response to IFX at maintenance therapy	
Complete response	46 (97.9%)
Partial response	1 (2.1%)
No response	0 (0.0%)
CDAI	
Before IFX injection	208.5 ± 66.5 (85–450)
After IFX injection	98.2 ± 26.6 (50–210)
PDAI	
Before IFX injection	12.5 ± 1.9 (9–17)
After IFX injection	3.4 ± 0.8 (2–5)
Recurrence rate	4 (8.5%)
Duration of recurrence, month	4.75 ± 2.06 (2.0–7.0)
Discontinuation of IFX	1 (2.1%)
Adverse events	
Perianal bleeding	1 (2.1%)
Skin eruption	1 (2.1%)

SD, standard deviation; IQR, interquartile; IFX, infliximab; CDAI, Crohn's disease activity index; PDAI, perianal Crohn's disease activity index.

and complex fistula groups. Although the PDAI values were not different between the two groups, PDAI after using infliximab were decreased more than before using infliximab in both groups ($P < 0.001$). In addition, patients in the complex fistula group had higher rates of perianal abscess than the simple fistula group (96.3% vs. 60.0%, $P = 0.003$). For the surgical treatment, seton drainage was performed most commonly in the two groups. 5-ASA was most commonly used with infliximab in both groups. Recurrence occurred in 5.0% of the simple fistula group and 11.1% of the complex fistula group. However, there was no statistical significance in the rate of concomitant surgery and medical therapies as well as recurrence between the two groups (Table 4).

4. Discussion

This study was focused to assess the treatment response of infliximab after combined surgical procedures in patients with fistulizing perianal Crohn's disease and to analyze them according to fistula subtypes. In our results, complete response after using infliximab was more rapid and higher rates of treatment response than the outcomes of the ACCENT-II trial.[3] The rate of complete response was 72.3% after induction therapy and 97.9% after maintenance therapy in this study. In addition, the perianal fistula was first closed within 6 weeks (median ± SD, 6.00 ± 8.00 (range, 5–13)) with an average 2.13 times use of infliximab. On the other hand, complete response of the ACCENT-II trial was 55% of patients at 6 weeks after induction therapy and 36% at 54 weeks after maintenance therapy.[3,7] Rasul et al. also reported that clinical fistula closure occurred in 49% of patients at 8 weeks and 46% at 56 weeks to use infliximab in patients with perianal fistulizing Crohn's disease.[13] However, it is noticeable that these studies were performed by using only infliximab without combining surgical procedures. Because surgical procedures such as seton drainage or fistulectomy has advantages to resolve tissue inflammation and improve the healing process, a combination treatment with surgery and infliximab can have better treatment responses and shorter times of healing than infliximab or surgery alone.[14–18] According to the comparative analysis by Sciaudone et al., patients who received combined treatments with infliximab had shorter times to healing of fistulas and longer times to relapse than surgery or infliximab alone.[15] In addition, a systemic review and meta-analysis for the treatment of perianal Crohn's fistula compared between seton drainage and anti-TNF agents reported that combined treatments showed significantly favorable outcomes in spite of various treatment responses.[19] In these regards, our results can be interpreted that a combination therapy with infliximab and surgery had advantages to treat fistulizing perianal Crohn's disease with effective and rapid healing rates.

Perianal fistulas can be classified by subtypes according to Park's classification. In this study, we divided patients into the simple and complex fistula groups because they can have different healing rates from infliximab according to locations and complexities of fistula subtypes. Although the rates of concomitant perianal abscess were higher in the complex fistula group than the simple fistula group, treatment responses were not significantly different during induction and maintenance therapies. In addition, recurrence rates, PDAI values, used numbers of infliximab and periods for the first fistula closure were not significantly different between the two groups. Because the complex fistula group is composed of complex fistulas with a high type such as a suprasphincteric fistula or extrasphincteric fistula, it can be expected that there are more difficulties to treat perianal fistulas of the complex fistula group than the simple fistula group. However, the clinical outcomes of these two groups were not significantly different as shown in Table 4. Adequate drainage of perianal abscess, resolving tissue inflammation and controlling septic conditions from proper surgical procedures might amplify the effect of infliximab to close perianal fistulas regardless of their subtypes. In these aspects, treatment response of infliximab can be comparable among fistula subtypes when surgical treatment is performed properly with infliximab.

Infliximab have been regarded as an alternative therapy to overcome limitations of conventional treatment for Crohn's disease. However, there were concerns for adverse

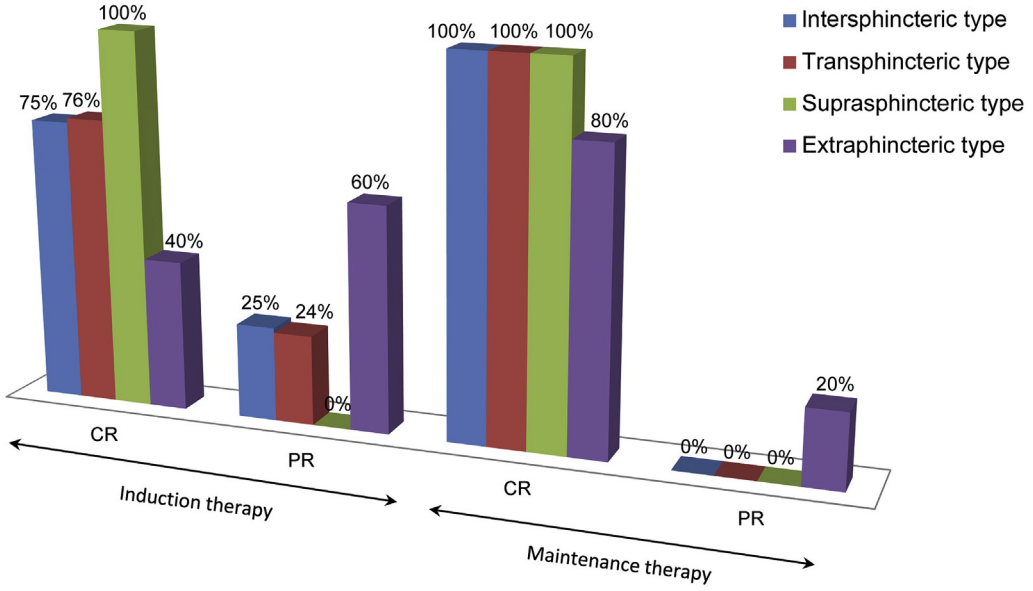

Figure 3 Treatment response of infliximab combined with surgical procedures according to fistula subtypes.

events associated with infliximab. There are various side effects related with infliximab such as headache, acute or delayed infusion reaction, leukopenia, serious infection, antichimeric antibody formation, and increased risk of malignancy.[20] Present et al. reported that headache, abscess formation, upper respiratory tract infection and fatigue were developed in patients who used 5 mg/kg of infliximab.[7] However, according to the ACCENT-II trial, the rate of serious adverse events was higher in the placebo group than the infliximab group (23% vs. 14%, P = 0.05). In addition, infection and infusion reaction associated with infliximab were not significantly different between the

Table 4 Subanalysis of the response according to fistula subtypes.

	Simple fistula group (n = 20)	Complex fistula group (n = 27)	P value
Time to the first fistula closure (week)	6.80 ± 4.66 (2–14)	8.41 ± 4.77 (2–23)	0.234[c]
Uses of IFX to the first fistula closure (times)	1.90 ± 0.79 (1–3)	2.30 ± 0.61 (1–4)	0.077[c]
Response to IFX after induction therapy			0.726[b]
Complete response	15 (75.0%)	19 (70.4%)	
Partial response	5 (25.0%)	8 (29.6%)	
Response to IFX after maintenance therapy			1.000[a]
Complete response	20 (100%)	26 (96.3%)	
Partial response	0 (0.0%)	1 (3.7%)	
PDAI (before IFX)	12.5 ± 1.64 (9.0–17.0)	12.5 ± 2.03 (9.0–17.0)	0.621[c]
PDAI (after IFX)	3.35 ± 0.75 (2.0–5.0)	3.37 ± 0.84 (2.0–5.0)	0.963[c]
Concomitant perianal abscess	12 (60.0%)	26 (96.3%)	0.003[a]
Concomitant surgical treatment			0.120[a]
Seton procedure	12 (60.0%)	22 (81.5%)	
Fistulotomy	4 (20.0%)	1 (3.7%)	
Fistulectomy	3 (15.0%)	1 (3.7%)	
Incision and drainage	1 (5.0%)	1 (3.7%)	
Seton + coring out fistulectomy	0 (0.0%)	2 (7.4%)	
Concomitant CD medication			0.198[a]
5-ASA	16 (80.0%)	22 (81.5%)	
5-ASA + AZP	1 (5.0%)	4 (14.8%)	
5-ASA + steroid	2 (10.0%)	0 (0.0%)	
5-ASA + AZP + steroid	0 (0.0%)	1 (3.7%)	
Only antibiotics	1 (5.0%)	0 (0.0%)	
Recurrence rate	1 (5.0%)	3 (11.1%)	0.626[a]

CD, Crohn's disease; ASA, aminosalicylate; AZP, azathioprine; IFX, infliximab; PDAI, perianal Crohn's disease activity index.
[a] Fisher's exact test.
[b] Chi-square test.
[c] Mann–Whitney *U* test.

Table 5 Previous studies with infliximab treatment for perianal Crohn's fistula.

No	Author	Year	Country	Concomitant therapy	No. of patients	Follow-up period (months)	Response assessment	Complete response (CR)	Partial response (PR)	Recurrence rate	Adverse event	Before PDAI	After PDAI	PDAI P value
1	Yang et al.	2015	China	Surgical & medical	28	26.4 (14–41)	30th week (after 6th injection)	89.3%	N/A	7.1%	7.1%	8.54 ± 4.89	0.93 ± 2.08	<0.01
2	Uchino et al.	2011	Japan	Surgical & medical	62 (IFX:n = 26, No IFX:n = 36)	N/A	12th–15th week	0%	88.5%	0%/5yr[a] 53.9%/5yr[b]	11.3%	11 (8–15)	6 (1–10)	<0.01
3	Hukkinen et al.	2014	Finland	Surgical & medical	13	16 (11–22)	6th week 8th week	23.1% 76.9%	69.2% 15.4%	23.1%	76.9%	35 (26–37)	20 (20–25)	N/A
4	Guidi et al.	2008	Italy	Surgical & medical	9	28 ± 16	6th week	88.9%	11.1%	22.2%	11.1%	11.5 ± 2.9	5.4 ± 2.2	<0.01
5	Hyder et al.	2006	UK	Surgical & medical	22	21 (4–31)	6th week	18%	36.4%	N/A	0%	11 (8–17)	8 (5–16)	<0.01
6	Antakia et al.	2011	UK	Surgical & medical	48	20	8th week	29%	42%	25%	6.3%	N/A	N/A	N/A
7	Topstad et al.	2002	Canada	Surgical & medical	21 (perianal)	10 (3–21)	6th week (After 3 doses of IFX)	66.7%	19%	19%	24.1%	N/A	N/A	N/A

PCD, perianal Crohn's disease; IFX, infliximab; PDAI, perianal Crohn's disease activity index.
[a] Cumulative incidence of fistula recurrence in patients without anorectal stricture.
[b] Cumulative incidence of fistula recurrence in patients with anorectal stricture.

infliximab and placebo groups.[3] In this study, we had 4.2% of the patients with side effects, which is a lower rate than previous studies. Discontinuation during the infliximab treatment was developed in one patient (2.1%) due to psoriasiform dermatitis, which can be developed by cutaneous eruption from autoimmune disease induced by infliximab.[20,21] There are limitations to assess adverse events from our small study population. However, because previous studies with large-scaled long-term outcomes showed favorable outcomes, it is considered that the use infliximab is safe and its efficacy might be superior to the side effects to treat Crohn's disease.[22]

The recurrence rate of this study was 8.5% during the study period. However, the ACCENT-II trial reported that the loss of response occurred in 42% of patients in the infliximab maintenance group.[3] As shown in Table 5, previous studies showed various recurrence rates with 7.1%–55.0%. In the systematic and meta-analysis from Groof et al., the recurrence rate was reported from 8.0% to 40.9%.[19] Because previous studies had different treatment protocols respectively, the heterogeneity of study designs tend to make it difficult to assess the recurrence rates. Although we had a lower rate of recurrence than published literatures, it is required to assess the recurrence rate again in the long-term follow-up period.

This study evaluated clinical characteristics of perianal Crohn's disease in Korean patients after using infliximab. As reported by published literatures, there are considerably different phenotypes and clinical manifestations of Crohn's disease between Eastern and Western countries.[11,23] Asian patients with Crohn's disease tend to be composed of dominantly males with a lower prevalence of cigarette smoking and familial history. In addition, there are higher proportions of perianal fistulas in Asian countries than in the West.[11,24,25] However, initial treatments using biologics, as called top-down therapy, are not performed frequently in Asian countries because of the economic burden on the national insurance system. Burisch et al. reported that biologics were used 7% in Western Europe and 2% in the Eastern as initial treatments during the first 3 months of Crohn's disease.[26] Although it is uncertain that treatment responses of biologics in Asian patients are more effective than Western, recent studies of Asian countries showed a rapid response to infliximab and favorable clinical outcomes. In the reports from China by Yang et al., 89.3% of patients with perianal fistulizing Crohn's disease had complete responses with an average of 31.4 days healing time.[16] Our results also support that infliximab can be effective to treat fistulizing perianal Crohn's disease as the initial treatment. More supportive data in Asian countries are needed to expand the top-down therapy as the first treatment.

There are several limitations of this study to assess the efficacy of infliximab for perianal Crohn's fistulas. The small number of the study population has the possibility to cause type II errors. In addition, because the median follow-up period of this study was 11.0 $\pm$ 8.0 months, it is needed to assess the rates of recurrence and adverse events in the long-term period. However, this study is meaningful because the treatment responses of infliximab combined with surgical procedures in the Korean patients with perianal Crohn's disease were evaluated according to fistula subtypes. Prospective, randomized controlled clinical trials for a combined surgical and infliximab treatment are required to support our results in the future.

In conclusion, infliximab combined with surgical procedures are efficacious and safe to treat fistulizing perianal Crohn's disease with rapid and favorable clinical outcomes. Moreover, treatment response of infliximab can be comparable regardless of fistula subtypes when surgical treatment is performed properly with infliximab. Because recurrence and adverse events occurred limitedly, it is expected that a combined surgical treatment with infliximab as top-down therapy can overcome the refractory characteristics of perianal fistulizing Crohn's disease.

Conflict of interest

The authors have no conflicts of interest or financial ties to disclose.

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References

1. Nielsen OH, Rogler G, Hahnloser D, Thomsen OO. Diagnosis and management of fistulizing Crohn's disease. *Nat Clin Pract Gastroenterol Hepatol*. 2009;6:92–106.
2. Schwartz DA, Loftus Jr EV, Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology*. 2002;122:875–880.
3. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med*. 2004;350:876–885.
4. Schwartz DA, Ghazi LJ, Regueiro M, et al. Guidelines for the multidisciplinary management of Crohn's perianal fistulas: summary statement. *Inflamm Bowel Dis*. 2015;21:723–730.
5. Tang LY, Rawsthorne P, Bernstein CN. Are perineal and luminal fistulas associated in Crohn's disease? A population-based study. *Clin Gastroenterol Hepatol*. 2006;4:1130–1134.
6. Schwartz DA, Pemberton JH, Sandborn WJ. Diagnosis and treatment of perianal fistulas in Crohn disease. *Ann Intern Med*. 2001;135:906–918.
7. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med*. 1999;340:1398–1405.
8. Topstad DR, Panaccione R, Heine JA, Johnson DR, MacLean AR, Buie WD. Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal Crohn's disease: a single center experience. *Dis Colon Rectum*. 2003;46:577–583.
9. Uchino M, Ikeuchi H, Bando T, et al. Long-term efficacy of infliximab maintenance therapy for perianal Crohn's disease. *World J Gastroenterol*. 2011;17:1174–1179.
10. Antakia R, Shorthouse AJ, Robinson K, Lobo AJ. Combined modality treatment for complex fistulating perianal Crohn's disease. *Colorectal Dis*. 2013;15:210–216.
11. Park SJ, Kim WH, Cheon JH. Clinical characteristics and treatment of inflammatory bowel disease: a comparison of

Eastern and Western perspectives. *World J Gastroenterol WJG*. 2014;20:11525.
12. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. *Br J Surg*. 1976;63:1—12.
13. Rasul I, Wilson SR, MacRae H, Irwin S, Greenberg GR. Clinical and radiological responses after infliximab treatment for perianal fistulizing Crohn's disease. *Am J Gastroenterol*. 2004; 99:82—88.
14. Regueiro M, Mardini H. Treatment of perianal fistulizing Crohn's disease with infliximab alone or as an adjunct to exam under anesthesia with seton placement. *Inflamm Bowel Dis*. 2003;9:98—103.
15. Sciaudone G, Di Stazio C, Limongelli P, et al. Treatment of complex perianal fistulas in Crohn disease: infliximab, surgery or combined approach. *Can J Surg*. 2010;53:299—304.
16. Yang BL, Chen YG, Gu YF, et al. Long-term outcome of infliximab combined with surgery for perianal fistulizing Crohn's disease. *World J Gastroenterol*. 2015;21:2475—2482.
17. Hyder SA, Travis SP, Jewell DP, Mc CMNJ, George BD. Fistulating anal Crohn's disease: results of combined surgical and infliximab treatment. *Dis Colon Rectum*. 2006;49:1837—1841.
18. Talbot C, Sagar PM, Johnston MJ, Finan PJ, Burke D. Infliximab in the surgical management of complex fistulating anal Crohn's disease. *Colorectal Dis*. 2005;7:164—168.
19. de Groof EJ, Sahami S, Lucas C, Ponsioen CY, Bemelman WA, Buskens CJ. Treatment of perianal fistulas in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-TNF treatment. *Colorectal Dis*. 2016;18:667—675.
20. Guo Y, Lu N, Bai A. Clinical use and mechanisms of infliximab treatment on inflammatory bowel disease: a recent update. *Biomed Res Int*. 2013;2013:581631.
21. Iborra M, Beltran B, Bastida G, Aguas M, Nos P. Infliximab and adalimumab-induced psoriasis in Crohn's disease: a paradoxical side effect. *J Crohns Colitis*. 2011;5:157—161.
22. Schnitzler F, Fidder H, Ferrante M, et al. Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. *Gut*. 2009;58:492—500.
23. Baik SH, Park KJ, Lee KY, et al. Characteristic phenotypes in Korean Crohn's disease patients who underwent intestinal surgery for the treatment. *J Korean Med Sci*. 2013;28:575—579.
24. Ye BD, Yang SK, Cho YK, et al. Clinical features and long-term prognosis of Crohn's disease in Korea. *Scand J Gastroenterol*. 2010;45:1178—1185.
25. Zeng Z, Zhu Z, Yang Y, et al. Incidence and clinical characteristics of inflammatory bowel disease in a developed region of Guangdong Province, China: a prospective population-based study. *J Gastroenterol Hepatol*. 2013;28:1148—1153.
26. Burisch J, Pedersen N, Cukovic-Cavka S, et al. East-West gradient in the incidence of inflammatory bowel disease in Europe: the ECCO-EpiCom inception cohort. *Gut*. 2014;63: 588—597.