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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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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

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