



Factors Affecting Surgical Treatment With Infliximab Therapy in Perianal Fistula With Crohn Disease

Jong Lyul Lee

Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

See Articles on Page 249-253

The presence of perianal fistula is a common manifestation of Crohn disease (CD) and is associated with an increased risk of complications, hospitalization, intestinal resection, and postoperative recurrence [1-3]. The 2005 Montreal World Congress of Gastroenterology decided to add the perianal modifier (p) to the Montreal classification as a predictor of poor prognosis [4]. Moreover, other studies have suggested that long-standing perianal fistula related to CD might be a risk factor for anorectal malignancy [5, 6]. A recent study and a meta-analysis demonstrated that perianal fistula in CD is more common in Asian patients than Caucasian patients [7, 8]. Treatment strategies for perianal fistula with CD need to be established.

A recent population-based study observed a significantly decreasing trend in the risk of proctectomy in the biologic era (1998 or after) compared with the prebiologic era (before 1998), and insisted that this trend reflected the possibility of a disease-modifying effect of biologics on the natural history of perianal fistula in CD [9]. Besides, not only natural course but also evidence-based guidelines and reviews have recommended the use of anti-tumor necrosis factor (TNF)- α agents for perianal fistula in CD [10-13]. However, many factors should be considered when using anti-TNF- α agents for perianal fistula in CD, including type of anal fistula (high vs. low or simple vs. complex), the presence of proctitis or anal stricture, whether the patient has definite surgical drain or not, use of antibiotics, and the timing, dose escalation, and maintenance period of anti-TNF- α agents [10-13].

Correspondence to: Jong Lyul Lee, M.D.
Department of Surgery, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-1732, Fax: +82-2-474-6027
E-mail: iamleejong@amc.seoul.kr
ORCID code: <https://orcid.org/0000-0002-5878-8000>

© 2019 The Korean Society of Coloproctology

This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

The timing of anti-TNF- α agents is one potential factor investigated by several studies. However, based on their findings, the start timing of anti-TNF- α agents does not seem to matter, consistent with the current study. Although the abovementioned studies defined the start timing as within 24 hours after surgery [14, 15], within a few weeks after surgery [16-18], or after the perianal infection had resolved [19], the effects of biologics were proven [14-19]. After all, it would seem important to control perianal infection with surgical intervention rather than the start timing of anti-TNF- α agents and the current study supports this conclusion. However, when investigating the importance of start timing of anti-TNF- α agents, researchers need to match other factors including anal fistula type, the presence of proctitis or anal stricture, whether the fistula is controlled or not, the definition of response and recurrence, evaluation method, and removal timing of seton drain.

The current study did not establish the type of anal fistula or the presence of rectal inflammation, and only included seton procedures. Although anti-TNF- α is recommended for the treatment of perianal fistula in CD with a high level of evidence [10-13], simple types of perianal fistula in the absence of rectal inflammation may resolve with surgical therapy (fistulotomy vs. ligation of internal fistulous tract) without anti-TNF- α treatment [20]. In addition, considering the need for maintenance of anti-TNF- α therapy and gradual resistance (resulting in a decreasing efficacy in ~50% of patients over time) [20], a therapeutic strategy of holding anti-TNF- α agents in reserve is needed for patients with simple perianal fistula without proctitis.

A great deal of evidence supports that an appropriate seton drain followed by anti-TNF- α agents therapy leads to favorable responses regardless of the start timing of anti-TNF- α agents. Further studies of perianal fistula in CD are needed to determine the appropriate evaluation and response method (e.g., van Assche index), timing of response assessment, decision-making related to anti-TNF- α agents (e.g., initiation indications, duration, specific anti-TNF- α agent, dose escalation, or change in timing), and the timing of seton removal.

REFERENCES

1. Bernell O, Lapidus A, Hellers G. Risk factors for surgery and post-operative recurrence in Crohn's disease. *Ann Surg* 2000;231:38-45.
2. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. *Gastroenterology* 2006;130:650-6.
3. Lakatos PL, Czegledi Z, Szamosi T, Banai J, David G, Zsigmond F, et al. Perianal disease, small bowel disease, smoking, prior steroid or early azathioprine/biological therapy are predictors of disease behavior change in patients with Crohn's disease. *World J Gastroenterol* 2009;15:3504-10.
4. Satsangi J, Silverberg MS, Vermeire S, Colombel JF. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;55:749-53.
5. Beaugerie L, Carrat F, Nahon S, Zeitoun JD, Sabaté JM, Peyrin-Biroulet L, et al. High risk of anal and rectal cancer in patients with anal and/or perianal Crohn's disease. *Clin Gastroenterol Hepatol* 2018;16:892-9.e2.
6. Lee HS, Park SH, Yang SK, Ye BD, Kim JH, Kim SO, et al. The risk of colorectal cancer in inflammatory bowel disease: a hospital-based cohort study from Korea. *Scand J Gastroenterol* 2015;50:188-96.
7. Song EM, Lee HS, Kim YJ, Oh EH, Ham NS, Kim J, et al. Incidence and outcomes of perianal disease in an Asian population with Crohn's disease: a nationwide population-based study. *Dig Dis Sci* 2019 Sep 4 [Epub]. <https://doi.org/10.1007/s10620-019-05819-9>.
8. Shi HY, Levy AN, Trivedi HD, Chan FKL, Ng SC, Ananthakrishnan AN. Ethnicity influences phenotype and outcomes in inflammatory bowel disease: a systematic review and meta-analysis of population-based studies. *Clin Gastroenterol Hepatol* 2018;16:190-7.e11.
9. Park SH, Aniwan S, Scott Harmsen W, Tremaine WJ, Lightner AL, Faubion WA, et al. Update on the natural course of fistulizing perianal Crohn's disease in a population-based cohort. *Inflamm Bowel Dis* 2019;25:1054-60.
10. Steinhart AH, Panaccione R, Targownik L, Bressler B, Khanna R, Marshall JK, et al. Clinical practice guideline for the medical management of perianal fistulizing Crohn's disease: the Toronto consensus. *Inflamm Bowel Dis* 2019;25:1-13.
11. Schwartz DA, Ghazi LJ, Regueiro M. Guidelines for medical treatment of Crohn's perianal fistulas: critical evaluation of therapeutic trials. *Inflamm Bowel Dis* 2015;21:737-52.
12. Panés J, Rimola J. Perianal fistulizing Crohn's disease: pathogenesis, diagnosis and therapy. *Nat Rev Gastroenterol Hepatol* 2017;14:652-64.
13. Kotze PG, Shen B, Lightner A, Yamamoto T, Spinelli A, Ghosh S, et al. Modern management of perianal fistulas in Crohn's disease: future directions. *Gut* 2018;67:1181-94.
14. Hyder SA, Travis SP, Jewell DP, McC Mortensen NJ, George BD. Fistulating anal Crohn's disease: results of combined surgical and infliximab treatment. *Dis Colon Rectum* 2006;49:1837-41.
15. Sciaudone G, Di Stazio C, Limongelli P, Guadagni I, Pellino G, Riegler G, et al. Treatment of complex perianal fistulas in Crohn disease: infliximab, surgery or combined approach. *Can J Surg* 2010;53:299-304.
16. Park EJ, Song KH, Baik SH, Park JJ, Kang J, Lee KY, et al. The efficacy of infliximab combined with surgical treatment of fistulizing perianal Crohn's disease: comparative analysis according to fistula subtypes. *Asian J Surg* 2018;41:438-47.
17. Uchino M, Ikeuchi H, Bando T, Matsuoka H, Takesue Y, Takahashi Y, et al. Long-term efficacy of infliximab maintenance therapy for perianal Crohn's disease. *World J Gastroenterol* 2011;17:1174-9.
18. Bouguen G, Hugué A, Amiot A, Viennot S, Cholet F, Nachury M, et al. Efficacy and safety of tumor necrosis factor antagonists in treatment of internal fistulizing Crohn's disease. *Clin Gastroenterol Hepatol* 2019 May 22 [Epub]. pii: S1542-3565(19)30549-X. <https://doi.org/10.1016/j.cgh.2019.05.027>.
19. El-Gazzaz G, Hull T, Church JM. Biological immunomodulators improve the healing rate in surgically treated perianal Crohn's fistulas. *Colorectal Dis* 2012;14:1217-23.
20. Lewis RT, Bleier JI. Surgical treatment of anorectal Crohn disease. *Clin Colon Rectal Surg* 2013;26:90-9.