A series of seton techniques involving “top-down therapy” for patients with Crohn’s disease who initially presented with perianal fistulas

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Abstract:
Objectives: We determined the outcomes of seton treatment through a series of techniques using biological agents (BIOs) in 18 patients with Crohn’s disease (CD) who initially presented with perianal fistulas.
Methods: The patients underwent seton drainage using three seton types: a Penrose tube for fistulas with massive purulent discharge, a vessel loop for a small amount of discharge, and a rubber band for unproductive fistulas. If the distal end of the fistula extended more than 4 cm from the anal orifice, the skin and subcutaneous tissue were dissected along the outer edge of the anal sphincter to divide the fistulous tract into two portions. One seton encircled the sphincter from the primary opening throughout the anal canal (medial seton), and the other was inserted through the distal tract outside the sphincter (lateral seton). A BIO was then introduced immediately. When discharge ceased, the Penrose tube or vessel loop was replaced sequentially with a rubber band, which was tied fittingly and subsequently removed in medial to lateral order.
Results: The mean interval between fistula onset and CD diagnosis was 2.1 years, and that between CD diagnosis and introduction of BIOs was 0.5 years. The mean follow-up duration was 4 years. The BIOs currently used were infliximab in 10 patients, adalimumab in 7, and ustekinumab in 1. The overall success rate was 94.4%, including unproductive fistulas in 10 (55.6%) patients and fistula disappearance in 7 (38.9%).
Conclusions: Our seton drainage techniques via the “top-down” approach represent a promising avenue for treating perianal fistulas in patients with CD.
Keywords:
Crohn’s disease, perianal fistula, seton, biological agents

Introduction
The basic therapeutic strategy for ordinary perianal fistulas is fistulotomy from the secondary opening to the primary crypt. However, such surgery may impair sphincter function if applied to the fistulas associated with Crohn’s disease (CD) because of their complexity, higher position of the primary opening, and insufficient wound healing1-3. Therefore,
long-term seton drainage is recommended in the practical guidelines proposed by the European Association of Crohn’s and Colitis Organisation8, the American Society of Colon and Rectal Surgeons9, and the Japanese Society of Gastroenterology10. However, the types of setons have not been mentioned clearly in these guidelines; moreover, the timing of seton removal remains controversial11. In a nationwide survey for the surgical management of perianal CD, Lee et al.7 stated that practical guidelines are required for treating perianal fistulas in CD.

The aim of the present study was to determine the efficacy of our series of therapeutic strategies consisting of seton placement, replacement, and removal with the use of biological agents (BIOs), which was formulated for patients who initially presented with perianal fistulas.

Methods

From January 2009 to December 2016, we assessed 25 patients without a previous diagnosis of CD or bowel surgery who presented with perianal fistulas suspected to be associated with CD. CD was suspected in these patients for the following reasons: (1) delayed wound healing and/or de novo abscess formation after incisional drainage or surgery in 9 patients, (2) primary opening not originating from the anal crypt in 5, and (3) coexistence of multiple primary and secondary fistulous openings in 11 (including duplicate patients). Among them, 18 BIO-naive patients (15 from Yokoyama Memorial Hospital and 3 from Saigusa Coloproctological Clinic) who met the Japanese diagnostic criteria for CD were enrolled in this study.

Among the 18 patients, 6 underwent incisional drainage and 3 underwent seton drainage before visiting our outpatient department. All patients underwent anorectal examinations under anesthesia (EUA) before CD diagnosis. At the first EUA, 2 patients had only simple fistulas and 16 had complex fistulas, according to the classification of the American Gastroenterological Association8,11. Low transsphincteric fistulas with multiple productive secondary openings were found in 11 patients, high transsphincteric fistulas in 7, high intersphincteric fistulas in 2, and suprasphincteric fistulas in 1 (including duplicate patients). No rectovaginal fistula was included.

We performed diagnostic workups on these patients. All patients underwent ileocolonoscopy (ICS), and two underwent additional small-bowel X-ray series or single-balloon enteroscopy because of a lack of diagnostic findings on ICS. On the basis of the findings, CD was diagnosed according to the Japanese criteria proposed by an intractable inflammatory bowel disease research group subsidized by the Ministry of Health, Labor, and Welfare of Japan11.

Surveyed items

For these BIO-naive patients, the following data were investigated: sex, smoking status, age at fistula onset, age at CD diagnosis, CD activity index (CDAI) score9 at BIO introduction and at latest administration, site of bowel disease, number of patients with rectal involvement, interval between fistula onset and CD diagnosis, interval between CD diagnosis and BIO introduction, follow-up period, type of first-placed seton, first-introduced and currently used BIOs, dose escalation and switching of BIOs, concomitant use of immunomodulators, number of setons first placed and location of their primary openings, number of patients who required additional seton drainage, interval between first seton placement and replacement with a rubber band, number of patients with complete seton removal, disease prognosis (including fistula and anorectal stricture assessment), and clinical fecal continence at last follow-up examination. Anorectal stricture was defined to have a diameter that was unable to allow passage of an examiner’s index finger. The CDAI score between pre- and post-BIO administration was statistically compared using the paired t-test.

The primary outcome measure was fistula healing and duration of seton drainage in patients whose setons were removed completely, as mentioned in the section “Evaluation of outcomes” below. Secondary outcome measures included the CDAI score between pre- and post-BIO administration, materials of the first-inserted seton, interval between CD diagnosis and BIO introduction, number of patients who required dose escalation or switching BIOs, and number of patients who required additional seton because of progressive local sepsis.

Types of setons and fistula-dividing techniques

Initially, under caudal or spinal anesthesia with the patient in the supine lithotomy position, all enrolled patients underwent anorectal examinations/seton drainage using one of three seton types: (1) a thin Penrose tube (Penrose drain AR3, A-No. 6; Fuji Systems Cooperation, Tokyo, Japan) for fistulas with purulent discharge spontaneously flowing from secondary openings or the deroofed portion, (2) a vessel loop (Vesseloop6, Maxxim Medical, Sugar Land, TX, USA) for purulent discharge detected on gentle finger compression, or (3) a rubber band (Fistula ligating rubber string8, Arakawa Medical Instrument Manufacturing Company, Tokyo, Japan) for unproductive fistulas or those with only serous exudates. When recurrent perianal sepsis occurred after the first seton placement, additional seton drainage was performed.

During the first seton placement, seton insertion through the primary opening was avoided as long as the primary lesion was not obviously opened without draining. When the distal end of a fistula extended more than approximately 4
Figure 1. Fistula-dividing technique.

(a) When the distal end of a fistula extended more than approximately 4 cm from the anal orifice, the skin was incised at the outer edge of the external sphincter muscle.

(b) Subsequently, subcutaneous tissue was dissected upward along the outer side of the sphincter to divide the fistulous tract into two portions for seton insertion; a black arrow shows the Penrose medial seton encircling the sphincter muscles from the primary opening throughout the anal canal, and a white arrow shows the lateral seton inserted through the distal fistulous tract outside the sphincter. However, insertion of the medial seton was avoided as long as the primary lesion was not obviously opened with draining.

(c) The seton was subsequently removed in order, from the medial to lateral setons. Using the railroad technique, the Penrose lateral seton was replaced with a rubber band, which was tied repeatedly with moderate tension to keep the rubber band fitted to the skin (“fittingly tied seton technique”).

(d) The “lateral seton” was finally removed when its fistulous tract migrated toward the skin, becoming a subcutaneous tunnel (gradual migration technique).

Replacement of the seton using the railroad and gradual migration techniques

Patients were followed regularly at least once per 4 weeks until all the setons were removed. After seton removal, they were followed up at least once per 8 weeks.

Thereafter, when cessation of discharge (dry anus) was confirmed with BIO administration as maintenance therapy, Penrose tubes were subsequently replaced with rubber bands using the railroad technique without anesthesia (Figure 2a-d). The rubber band setons were removed gradually in order, from the medial to lateral setons (Figure 1c). The lateral seton was tied repeatedly with a 3-0 braided nylon suture to

cm from the anal orifice, the skin was incised at the outer edge of the sphincter muscle, and the subcutaneous tissue was dissected upward along the outer edge of the sphincter to divide the fistulous tract into two portions for seton insertion: one seton encircled the sphincter muscles from the primary opening throughout the anal canal (“medial seton”), and the other seton was inserted through the distal fistulous tract outside the sphincter (“lateral seton”); we termed this the fistula-dividing technique (Figure 1a, b). Medial and lateral setons were tied in the same manner for drainage.
attach the seton to the skin with moderate tension so that it abutted the enclosed tissue with only minimal tension without significant pain (“fittingly tied seton technique”). Every 4-8 weeks, it was retied if it had become loose. Finally, the residual lateral seton was removed when the fistulous tract migrated toward the skin, becoming a subcutaneous tunnel (gradual migration technique, Figure 1d). When a vessel loop was used, after cutting the loop, the edges of the vessel loop and a new rubber band were tied with a 3-0 braided nylon suture so that the vessel loop could be replaced easily by the rubber band by pulling the other edge of the loop.

**Introduction, dose escalation, and switching of BIOs**

We used three BIOs: infliximab (IFX) was introduced first until August 2013, adalimumab (ADA) was used between September 2013 and May 2017, and ustekinumab (UST) was initiated after that. These BIOs were administered as soon as possible after EUA/seton placement.

When we could not achieve a significant reduction in fistula discharge, the dose of IFX or ADA was intensified. If such dose escalation did not work sufficiently or any adverse effect or paradoxical reaction of BIOs was confirmed, a switch to another BIO was attempted thereafter.

**Evaluation of outcomes**

After seton removal, complete closure of the primary opening with scarring detected on proctoscopy was regarded as mucosal healing. We evaluated fistula outcome on the basis of the Fistula Drainage Assessment at each study visit, and fistula prognosis was categorized into three groups (active, in remission, and healed). If obvious discharge from the fistula was noted, it was regarded as active; if the fistula no longer drained despite gentle finger compression, it was defined as being in remission; and if the fistula was not palpable, with mucosal healing of the primary opening and closure of the secondary opening after seton removal, it was categorized as healed.

At the patients’ last hospital visit, rectal digital examination was performed to inspect for anorectal strictures, and fecal continence was evaluated clinically.

**Compliance with ethical standards**

Ethical approval: This clinical study was approved by the ethical review board of the Japan Medical Association (No. 29-01). Informed consent was obtained from all individual participants included in the study.
Patient demographic and treatment details are shown in Table 1.

Azathioprine (25 mg/day) was introduced in 10 patients, all of whom initially received IFX. Among them, it was withdrawn successfully once in 8 patients because of the absence of fistulous discharge during the course, 3 of whom required re-administration of azathioprine for reactive fistula. The other 2 patients received the same dose consecutively.

The overall number of primarily placed setons was 61, of which 22 were inserted through the primary opening and the other 39 were placed between secondary openings. Among the 22 setons at primary openings, 10 (45.5%) were located at the anal crypts, and the other 12 (54.5%) were placed at mucosal lesions apart from the crypts. Among the latter 12 setons, 6 passed through rectal ulcers positioned cephalad to the dentate line, 4 were placed through a cavitating ulcer occurring above or close to the dentate line, and the other 2 were inserted to the ulcer below the dentate line. The No. 6 Penrose tube used was placed through the anorectal primary lesion, but not the primary crypt. The vessel loop or rubber string was used for draining the anal crypt. A total of 15 (83.3%) patients had at least one seton passing through the internal openings (range, 1-3), and 11 (61.1%) had at least one fistula originating from a noncrypt primary opening. The primary openings were posterior in 9 (40.9%) patients, lateral in 8 (36.4%), and anterior in 5 (22.7%).

Eleven patients, including all three smokers and four of five patients with rectal involvement, required additional seton drainage (total, 25 times) because of recurrent local sepsis within a mean interval of 4.5 years (range, 2.5-6.5 years) after initial seton placement. All these setons were of the lateral type, and no medial seton was placed additionally. At the last follow-up, the total number of indwelling setons had declined from 61 to 9 (14.8%).

The fistula-dividing technique was applied for six fistulous tracts in five patients, all of whom underwent Penrose seton drainage. Among them, four patients achieved remission, but only one was healed.

A total of 15 patients (83.3%) with Penrose or vessel-loop setons received rubber seton replacements within a mean period of 1 year (range, 0.1-3.5 years).

Regarding primary outcome, all setons were removed successfully in 10 patients (55.6%) within a mean duration of 2.6 years (range, 1.4-5.7 years), and 7 (38.9%) of them reached healed status. Among the 7 patients who were cured, 2 had crypt-originated and the others had noncrypt-originated fistulas. No patient who became seton free experienced de novo sepsis during a mean interval of 0.8 years (range, 0.1-2.6 years) after complete seton removal. Finally, 7 patients with setons achieved remission; thus, 17 patients achieved healed or remission status, for an overall success rate of 95.5%.

Regarding secondary outcome, CDAI score between pre- and post-BIO administration, materials of the first-inserted seton, interval between CD diagnosis and BIO introduction, and number of patients who required dose escalation or switching BIoS are shown in the Table 1.

Anorectal strictures or any impairment of fecal continence was not observed at the latest follow-up.

IFX was first introduced in 12 (66.7%) patients, ADA in 5 (27.8%), and UST in 1 (5.6%). Three patients receiving IFX switched to ADA because of infusion reactions or paradoxical reactions, such as hidradenitis suppurativa. One patient receiving ADA switched to IFX because of palmoplan-
tar pustulosis. Finally, IFX was administered in 10 (55.6%) patients, ADA in 7 (38.9%), and UST in 1 (5.6%). Dose escalation was required in 3 patients (IFX, 2; ADA, 1) because of insufficient response. Among them, 1 was healed with IFX, whereas the other 2 achieved remission.

**Discussion**

Widespread early use of BIOs cannot be recommended for all CD patients, but for patient subgroups with a predicted disabling course (such as those with extensive disease, severe rectal disease, young age, severe perianal disease, and steroid requirement at diagnosis)\(^{(15)}\), the early introduction of a BIO can be considered\(^{(16)}\). Long-term treatment goals for perianal lesions associated with CD are to maintain sphincter function and avoid anorectal stenosis and carcinoma, which may occur as sequelae of persistently active CD\(^{(14,16)}\). Therapeutic intervention should be applied promptly before such irreversible complications occur. Accordingly, early administration of BIOs may be feasible, which could alter the natural course of CD\(^{(23)}\). Rayen et al.\(^{(17)}\) reported that 13% of patients with perianal fistulas who received BIOs demonstrated complete healing on clinical evaluation.

In patients being treated with BIOs for fistula closure, the timing of seton removal is controversial. In the randomized ACCENT 2 trial, setons were removed at 2 weeks after starting IFX, and this resulted in new abscesses developing in 15% of patients\(^{(18)}\). Hence, some studies have suggested retaining setons at least until the induction period of IFX has been completed\(^{(10)}\). The decision to remove a seton must be balanced with the knowledge that long-term healing with this strategy occurs in only approximately 40% of patients\(^{(19)}\). In the present study, although 10 patients (55.6%) needed 2.6 years on average to be free from the seton, they did not require additional drainage thereafter. Therefore, the timing of seton removal was considered to be appropriate. However, 1 patient required as long as 5.7 years for seton removal. To shorten the period of an indwelling seton, a Penrose drain should be replaced with a rubber band as soon as possible if the fistula becomes unproductive, and for that purpose, dose intensification, interval shortening, or eventually switching of BIOs should be done promptly without delay if the fistula is persistently active.

In our study, as many as 11 patients required additional seton placement repeatedly to control local sepsis despite BIO maintenance therapy, including all 3 smokers and 4 of 5 patients with rectal involvement. Smoking is an independent risk factor associated with postoperative surgical recurrence under BIO maintenance therapy\(^{(20)}\). Active proctitis is not only a risk factor for perianal fistulizing disease but also a predictive factor for refractory, recurrent disease requiring proctectomy eventually\(^{(3)}\).

Although fistulotomy is a justifiable option for simple low fistulas without active colorectal disease\(^{(21,22)}\), some studies have described at least some degree of incontinence in >50% of patients in addition to delayed wound healing\(^{(12)}\). CD patients possibly are prone to sphincter function deterioration as a sequela of radical surgery and because of malnutrition. Thus, our seton treatment techniques were not followed by fistulotomy in order to preserve entire internal sphincter muscle.

Two mechanisms have been postulated with regard to the pathogenesis of CD fistulas: extension of rectal inflammation through ulcers and crypt-glandular infection\(^{(25)}\). Among 7 of our patients who were cured, 2 had crypt-originated and the others had noncrypt-originated fistulas. Our strategy is a justifiable option regardless of the pathogenesis of fistula formation in CD. However, we did not use No. 6 thinner Penrose drains for primary productive anal crypts as a result. Through this study, when a medial seton is necessary, a vessel loop or rubber string is more suitable for draining not only the anal crypt but also the primary mucosal lesion, because mucosal healing could be achieved with the use of BIO anyway.

If the anorectal primary lesion attains mucosal healing with BIO administration and the distal part of the fistulous tract becomes superficial with a seton, this would be an ideal treatment method on the basis of two factors: curability and preservation of sphincter function. Our therapeutic strategies were formulated on the basis of such ideas.

After seton drainage, an aggressive top-down strategy was advocated instead of a step-up approach, supported by evidence that the early use of BIOs induces higher remission rates for anorectal complex fistulas associated with CD\(^{(15,24)}\). Ma et al.\(^{(25)}\) mentioned that the early initiation of IFX or ADA within the first 2 years of diagnosis reduces the rate of surgery and secondary loss of response, which requires dose escalation. Additionally, a long disease duration of >1 year between CD diagnosis and first IFX administration is a risk factor for sustained clinical remission after the discontinuation of BIOs\(^{(26)}\). We previously reported that proactive gastrointestinal tract examination based on a high index of suspicion of CD prompted by the detection of an initial anorectal fistula could be expected to yield a high detection rate of early CD lesions\(^{(27)}\). In this study, all the enrolled patients had anorectal fistulas with an earlier age of onset, and BIOs were induced at a mean of 0.5 years after CD diagnosis. The high success rate of this series should be credited partly to the fact that therapeutic intervention was introduced promptly in earlier phases of the disease.

Tanaka et al.\(^{(20)}\) reported that drainage setons were completely removed successfully in 11 (78.6%) of 14 patients under IFX infusion during a 12.1-month mean follow-up period. In most patients, seton drains were removed completely after five rounds of IFX infusion. We could remove
all setons in 10 patients without recurrent sepsis after complete seton removal under BIO maintenance therapy.

Hanley et al. used a rubber band seton for the surgical management of anterior perianal fistulas, with good functional results. Division of the tissues was followed by scar formation proximal to the ligature. Thus, use of the Penrose drain during the period of a high flow of discharge was considered ideal, followed by replacement with a fittingly tied rubber band after discharge had ceased.

To the best of our knowledge, no study has reported on this series of management techniques for perianal fistulas associated with CD. No anorectal stenosis or impairment of fecal continence was observed, indicating that the sphincter function was adequately preserved through our surgical intervention methods.

Inatsugi et al. reported good outcomes using the separated loose seton drainage technique with BIO administration and seton removal in medial to lateral order. We removed setons in the same manner, and this strategy was considered justifiable for the following reasons: (1) even though 1 patient required additional drainage, all of them underwent “lateral” seton placement, but no “medial” seton was needed, (2) no patient who became seton-free experienced de novo sepsis after seton removal, and (3) 5 of 11 patients with a noncrypt primary opening achieved and maintained healed status with mucosal healing without recurrent sepsis.

We created the fistula-dividing technique along with BIO administration to cure the primary opening, and the distal part of the fistulous tract was to be healed using a fittingly tied seton constituting an elastic band. Seow-Choen described the railroad technique for seton placement. Because a rubber band is much thinner than a Penrose tube, it can be passed easily through the lumen of the Penrose tube, and the Penrose tube can be removed thereafter. This procedure did not require any anesthesia because of the lack of significant pain; thus, replacement with rubber bands can be performed easily and quickly in clinics.

Although the success rate of this study was satisfactory including a significant decrease of CDAI score between pre- and post-BIO administration, there were two critical problems in our results: (1) 8 patients could not become free of the seton and (2) the long-term prognosis for the 10 patients who were completely seton free is uncertain. We should pay careful attention to these patients while taking into consideration the dose intensity or need for switching BIOs and timing of seton removal.

In conclusion, our series of techniques for seton placement, replacement, and removal according to the top-down strategy represents a promising avenue for patients with CD who initially present with anorectal fistulas. However, further investigation is needed to confirm the long-term fistula activity and anal sphincter function and to prevent anorectal strictures, considering the limited follow-up period of this study and the secondary loss of response of BIOs.

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Conflicts of Interest
There are no conflicts of interest.

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