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Vavricka, S R ; Rogler, G

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Fistula Treatment: The Unresolved Challenge

Stephan R. Vavricka Gerhard Rogler

Division of Gastroenterology and Hepatology, Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland

Key Words
Anti-TNF agents · Ciprofloxacin · Crohn's disease · Fistula · Metronidazole

Abstract
In population-based studies, up to 50% of patients with Crohn's disease suffer from fistulas. Fistulas pose a considerable morbidity including permanent sphincter and perineal tissue destruction as well as professional and personal disabilities. Treatment options have progressed in recent years and fistula closure and fibrosis of the fistula track is achieved in some patients. Depending on severity of symptoms and fistula location, different medical and surgical therapies can be chosen. Internal fistulas such as ileoileal or ileocecal fistulas are either asymptomatic and do not require intervention or they are symptomatic and need surgery alone. They always carry a risk of abscess formation. Symptomatic perianal fistulizing disease can be treated with antibiotics (i.e. metronidazole and ciprofloxacin) for three months and/or immunosuppressant therapy (6-mercaptopurine or azathioprine). More complex cases require therapy with anti-TNF agents. Only few and preliminary data exist on cyclosporine A, tacrolimus or methotrexate in fistulizing Crohn's disease. Therefore, these therapies should mainly be used as second-line therapies. Surgery is reserved for the treatment of perianal sepsis in the presence of abscesses and refractory disease or complications of fistulas, or used in combination with pharmacological approaches. The surgical interventions in perianal disease consist of surgical drainage with or without seton placement, transient ileostomy, or in severe cases, proctectomy. The classification of fistulas in patients with Crohn's disease remains poorly defined and largely investigator dependent. The unresolved challenges in fistula treatment warrant randomized controlled trials for existing and future treatment strategies as well as a better classification system to compare available studies.

Introduction

Fistulas in Crohn's disease (CD) patients are often troublesome, mainly because of the limited treatment options available. These fistulas often cause impairment in quality of life for CD patients, with serious clinical and psychological consequences. In population-based cohorts, the cumulative incidence of fistula formation has been evaluated between 17 and 50% [1–6]. In a study following Crohn's patients between 1970 and 1995, Schwartz et al. reported a fistula occurrence of 35% over time [3]. Of those fistulas, 54% were perianal, 24% enteroenteric, 9% rectovaginal, and 13% involved other locations such as enterocutaneous, enterovesical, and intraabdominal fistulas. In this study, the cumulative incidence of fistulas was 33% 10 years after the diagnosis of CD and 50% after

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Stephan R. Vavricka, MD
Division of Gastroenterology and Hepatology, Stadtspital Triemli
Birmensdorferstrasse 497
CH–8063 Zurich (Switzerland)
Tel. +41 44 466 1317, Fax +41 44 466 2905, E-Mail stephan.vavricka@usz.ch

20 years [3]. One third of these patients had recurrent fistulas, which emphasizes the extent of this complication in patients with CD. Crohn's fistulas are thought to derive either from the anal glands at the dentate line in the anal canal or from ulcerations in the anus or rectum. Infections lead to abscess formation and subsequent tracking away from the anal canal. Fistulas are usually the consequence of penetration of an abscess into an adjacent organ or the skin. Thus, a fistula may initially present as an abscess, which upon spontaneous draining evolves into a fistulous tract.

Fistulas can present with persistent anal pain, painful defecation, and as perianal openings with purulent discharge. In approximately 10% of patients, perianal fistulisation is the initial manifestation of CD [5]. In some cases the formation of perianal fistulas might even precede the onset of CD by several years [5]. The fistulous openings most commonly involve the perianal skin, but can also be in the groin, vulva, or scrotum.

Fistulas can be classified based upon their anatomic extensions: simple fistulas are low (below the dentate line), have a single external opening, and are not painful with no evidence of rectovaginal fistula and with no evidence of anorectal stricture. Complex fistulas are high (above the dentate line), may have multiple openings, are fistulas with evidence of abscess, and may be associated with pain, with the presence of a rectovaginal fistula, anorectal stricture or active rectal disease at endoscopy [7].

The risk of fistula development is higher in patients with colonic CD, in particular in those with rectal involvement, as compared with patients without colorectal disease. Diagnosis and treatment of fistulas in CD patients is often difficult. Once a patient with CD develops a fistula, achieving healing is a lengthy process and multiple relapses can be expected. With improvement of diagnosis and treatment over the last decade, the prospect changed dramatically. While 10 years ago, the goal of treatment was improvement of fistula drainage, this changed in our days to complete cessation of drainage or even fistula closure. Treatment has furthermore become a combined effort between medical physicians and surgeons. The aim of this article is to review mainly pharmacological strategies that have been investigated in treatment of fistulizing CD. Some surgical strategies will be covered. One has to bear in mind that most published studies on fistulizing CD deal with therapy of external fistula (e.g. perianal) whereas data on therapy of internal fistula (e.g. enterovesical, enterouterine, or enterovaginal) are scarce.

Assessment and Scoring of Fistula in CD

The Crohn's Disease Activity Index (CDAI) [8] is often used in clinical trials. In the assessment of fistulas, however, this scoring system is not regarded as appropriate [9]. For instance, the CDAI only attributes 20 points to fistula regardless of the number and type of fistula. In 1980, Present et al. proposed a score investigating the reduction or closure of external fistulas [10]. This scoring system has not been validated in subsequent studies. In 1995, an index to measure severity of fistulas in CD patients – the Perianal Disease Activity Index – was published [11]. This score comprises five categories (discharge, pain, restriction of sexual activity, type of perianal disease, and degree of induration). It has been validated in patients undergoing treatment with metronidazole [11, 12]. Furthermore, this index was used as a secondary end-point in the placebo-controlled trial of infliximab for the closure of perianal fistulas [13]. Other therapeutic trials have used the finger compression technique to assess fistulas in CD [10, 13–15]. This primary efficacy endpoint was defined as a reduction of 50% in the number of draining fistulas observed in two or more consecutive visits as assessed by the study investigator using gentle finger compression. Although this technique is very investigator dependent, it has been used in several placebo-controlled trials with infliximab, and tacrolimus [13, 17, 27]. Studies that assess the reproducibility of this method compared with that of the PDAI are still desperately required. Thus, at this stage, there is no widely accepted and validated scoring system for fistulas in CD. The definition of 'response to therapy' varies from study to study. Furthermore, there is no consensus on when a fistula can be considered healed. This point is very crucial since several studies have demonstrated that fistula tracts persist after fistula closure and that completely healed fistulas can re-open after cessation of therapy [13, 16, 17].

Medical Therapies

A summary of different studies on medical therapy options in fistulizing CD is shown in table 1 [10, 12, 13, 15, 17–36].

Table 1. Summary of medical therapy options in fistulizing CD

First author	Drug	Regime	Study type	Year	Patients	Outcome	Study period
Antibiotics							
Bernstein [18]	metro	20 mg/kg/day	open label	1980	21	Clinical response (21/21) within 8 weeks; 56% (10/18) complete healing	10 weeks
Brandt [19]	metro	20 mg/kg/day	follow-up study of [30]	1982	26	metro could only be successfully discontinued in 28% (5/18) of patients	up to 36 months
Jakobovits [20]	metro	1,000–1,500 mg/day	open label	1984	8	20-fold reduction of draining fistulas; 50% reduction of detectable fistulous openings	up to 6 months
Thia [21]	cipro metro	1,000 mg of either drug	RCT	2009	25	Reduction of >50% draining fistula: 30% (3/10) cipro, 0% (0/7) metro, 12.5% (1/8) placebo	10 weeks
Dejaco [12]	metro + cipro + AZA	cipro: 500–1,000 mg/day metro: 1,000–1,500 mg/day for 8 weeks AZA: 2–2.5 mg/kg/day	open label	2003	52	Reduction of >50% draining fistula: 48% AZA and metro/cipro, 15% metro/cipro only	20 weeks
West [22]	cipro + IFX	cipro (1,000 mg/day) + IFX (5 mg/kg in week 6, 8, 12)	RCT	2004	24	Reduction of >50% draining fistula: 73% (8/11) cipro + IFX, 39% (5/13) IFX alone	18 weeks
Immunosuppressive agents							
Present [10]	6-MP	1.5 mg/kg/day	RCT	1980	36 (40 fistulas)	31% (9/29) closure in 6-MP, 6% (1/17) in placebo	52 weeks
Pearson [23]	6-MP, AZA	n.a.	meta-analysis of 5 trials	1995	70 with fistulas	Response rate (decreased discharge): 54% (22/41) AZA/6-MP, 21% (6/29) placebo	n.a.
Egan [24]	cyclo	4 mg/kg/day i.v., then p.o.	retrospective	1998	9	77% (7/9) partial response	up to 22 weeks
Hanauer [25]	cyclo	4 mg/kg/day i.v. for 6–10 days, then 8 mg/kg/day p.o.	retrospective (?)	1993	5 (12 fistulas)	83% (10/12) complete resolution	up to 18 months
Present [26]	cyclo	4 mg/kg/day i.v., then 6–8 mg/kg/day p.o.	open label	1994	16	88% (14/16) initial response, 44% (7/16) closure of fistulas	up to 37 months
Sandborn [27]	tacro	0.2 mg/kg/day or placebo	RCT	2003	48	Reduction of >50% draining fistula (improvement): 43% (9/21) tacro, 8% (2/25) placebo Healing: 10% (2/21) tacro, 8% (2/25) placebo	10 weeks
González-Lama [28]	tacro	0.05 mg/kg every 12 h	open label	2005	10	40% (4/10) complete clinical response, 50% (5/10) partial response	up to 24 months
Mahadevan [29]	MTX	25 mg/week i.m. for 3 months, then p.o.	retrospective chart review	2003	16	25% (4/16) complete closure, 31% (5/16) partial closure	n.a.
Anti-TNF agents							
Present [13]	IFX	5 or 10 mg/kg or placebo at weeks 0, 2, and 6	RCT	1999	94	Reduction of >50% draining fistula: 62% (39/62) IFX, 26% (8/31) placebo Complete closure: 46% (29/63) IFX, 13% (4/31) placebo	18 weeks
Sands [17]	IFX	5 mg/kg at weeks 0, 2, and 6, then every 8 weeks	RCT	2004	195 with IFX response at week 10/14	Reduction of >50% draining fistula: 46% (42/91) IFX, 23% (23/98) placebo Complete response: 36% (33/91) IFX, 19% (19/98) placebo	54 weeks

Table 1 (continued)

First author	Drug	Regime	Study type	Year	Patients	Outcome	Study period
Hanauer [30]	ada	weeks 0/2: 40 mg/20 mg s.c.; 80 mg/40 mg s.c.; 160 mg/80 mg s.c.	RCT	2006	32 with fistulas	Improvement: 75% (3/4) on 40/20 mg 20% (2/10) on 80/40 mg 8% (1/12) on 160/80 mg 33% (2/6) on placebo Remission: 75% (3/4) on 40/20 mg 0% (0/10) on 80/40 mg 0% (0/12) on 160/80 mg 17% (1/6) on placebo	4 weeks
Sandborn [31]	ada	160 mg s.c. week 0, 80 mg week 2	RCT	2007	45 with fistulas	Fistula improvement: 15% (3/20) ada, 20% (5/25) placebo Remission: 5% (1/20) ada, 8% (2/25) placebo	4 weeks
Colombel [32]	ada	80 mg/40 mg weeks 0/2, 40 mg e.o.w. or e.w.	RCT	2007	117	Complete closure: 33% (23/70) ada 13% (6/47) placebo	56 weeks
Colombel [33]	ada	80 mg s.c. week 0, 40 mg s.c. week 2, then 40 mg e.o.w. or e.w.	open label extension of [36]	2009	117	Sustained fistula healing: 90% (28/31) ada	2 years
Sandborn [34]	CZP	400 mg s.c. weeks 0, 2, 4, then every 4 weeks	RCT	2007	107 with fistulas	Fistula closure: 30% (14/46) CZP 31 (19/61) placebo	26 weeks
Schreiber [35]	CZP	400 mg s.c. weeks 0, 2, 4, then every 4 weeks	RCT	2007	58 with fistulas	Fistula closure: 54% (15/28) CZP 43% (13/30) placebo	26 weeks
Schoepfer [15]	CZP	400 mg s.c. weeks 0, 2, 4, then every 4 weeks	open label	2009	11 with fistulas (total 27 fistulas)	Reduction of >50% draining fistula: 72% (8/11)	6 weeks
Other medical therapies							
Fukuda [36]	oral spheric adsorptive carbon (AST)	2 g t.i.d. for 8 weeks	RCT	2008	57	Improvement: 37% (10/27) AST, 10% (3/30) placebo Remission: 29.6% (8/27) AST, 6.7% (2/30) placebo	8 weeks

All randomized controlled trials (RCT) were double-blind and placebo-controlled.

metro = Metronidazole; cipro = ciprofloxacin; AZA = azathioprine; 6-MP = 6-mercaptopurine; cyclo = cyclosporine A; tacro = tacrolimus; MTX = methotrexate; IFX = infliximab; ada = adalimumab; CZP = certolizumab pegol; e.o.w. = every other week; e.w. = every week.; t.i.d. = three times a day.

Placebo Effect

Uncontrolled studies evaluating fistula response to treatment should be considered with caution since the natural history of fistulas is unpredictable. In placebo-controlled trials a considerable response rate in the placebo arm has been observed in fistula treatment [10, 13, 27]. This has further been confirmed in a meta-analysis by Pascua et al., who reported an expected spontaneous fistula closure rate under placebo-therapy of 10% [37].

Aminosalycilates and Corticosteroids

5-aminosalicylic acid has not been shown to be effective [38] and should not be used in treatment of fistulizing CD [39]. Glucocorticoids are an effective treatment for flares in CD patients. However, their use in fistula therapy in CD patients is limited. Studies evaluating corticosteroid treatment in CD patients with fistulas showed an even worse outcome regarding fistula activity and need for surgery in the corticosteroid treatment group when compared to patients not taking steroids [40–42].

Antibiotics

Antibiotics are efficacious in the short-term management of fistulas and their associated infections, but the recurrence rate at withdrawal is high and complete healing is not frequently achieved with antibiotics alone. Nevertheless, antibiotics represent a widely-used first-line treatment option for fistulas in CD patients. Despite their widespread use, not many controlled trials regarding efficacy in the treatment of fistulizing CD have been published. The most widely used antibiotic is metronidazole [18–20, 43]. When metronidazole is used, a response can be expected after 6–8 weeks. The therapy usually is continued for 3–4 months. Metronidazole was shown to close fistulas in up to 83% in an open-label case series [18]. Although useful in short-term treatment, there are problems associated with long-term use of metronidazole. These include nausea, glossitis, metallic taste, and disulfiram-like response to alcohol intake. Particularly at higher doses (>750 mg daily), peripheral neuropathy and paresthesias limit the use of this agent for long-term treatment [19].

Ciprofloxacin has only been evaluated for the treatment of perianal CD in small, uncontrolled studies [44, 45]. Headaches, nausea, diarrhea and rash are known adverse reactions with ciprofloxacin. Spontaneous tendon rupture (Achilles tendon) has also been reported in patients using long-term ciprofloxacin [46]. There are no long-term fistula closure data supporting the use of antibiotics and withdrawal of antibiotics leads to re-exacerbation of the disease. Therefore, the use of antibiotics in combination with other therapies has been evaluated. An open-label prospective study was designed to treat patients with metronidazole and ciprofloxacin for 8 weeks. Some of the patients were already on azathioprine therapy, whereas others started on azathioprine after 8 weeks of antibiotic therapy [11]. Based on their results, the authors conclude that antibiotics might provide a bridge strategy for azathioprine therapy. Using ciprofloxacin in combination with infliximab was recently evaluated in a double-blind placebo-controlled study [22]. All patients received infliximab and were randomized to receive either ciprofloxacin of placebo. There was a trend for patients treated with ciprofloxacin to respond more than those on placebo therapy (OR = 2.37, p = 0.07) suggesting that ciprofloxacin in combination with infliximab may be more effective than infliximab alone.

Immunosuppressive Agents

Present et al. described the efficacy and safety of 6-mercaptopurine in the treatment of CD [47]. Among this collective, 40 fistulas were observed in 36 patients. Thirty-one percent of the fistulas closed completely during the treatment with 6-mercaptopurine, versus only 6% with placebo. The onset of response was often delayed, with 32% of the patients taking longer than three months to respond. A meta-analysis of the controlled trials with 6-mercaptopurin and azathioprine in CD that included patients with fistulas has shown a response rate to these drugs of 54% compared with 21% for placebo [23]. We can conclude from these studies that immunosuppression with azathioprine or 6-mercaptopurine is effective both in closing and in maintaining closure of fistulas. The doses should be at 2.0–3.0 mg/kg/day of azathioprine and 1.5mg/kg/day of 6-MP. Nevertheless, those agents produce fistula closure in only a minority of patients, but inflammation, discharge and discomfort often are reduced markedly. Adverse events include pancreatitis (3%), allergic reactions, infections, leucopenia, and drug-induced hepatitis. Intravenous cyclosporine [24–26] and oral tacrolimus [27, 28, 48] both improve or heal a substantial proportion of patients short-term, but they often relapse on stopping the drug. A study evaluating intravenous cyclosporine (4mg/kg/day) showed that 14 out of 16 patients (88%) responded. Complete closure was observed in 7 (44%) and a moderate improvement in the other 7 (44%) [26]. Two other uncontrolled studies obtained similar results [24, 25]. Clinical response was seen as soon as one week in those studies, but transition to oral therapy or discontinuation of cyclosporine was associated with a high relapse rate. Based on these studies, cyclosporine can be used in the treatment of fistulizing CD, but only as a bridging therapy to azathiorpine/6-mercaptopurine or methotrexate therapy. The side effects of cyclosporine include: hypertension, headache, hirsutism, hypertrichosis, seizure, hypertriglyceridemia, nausea, gingival hyperplasia, tremor, paresthesia, increased incidence of infection and nephropathy [49]. The only controlled trial of oral tacrolimus (0.2 mg/kg/day) showed a significantly positive effect on improvement compared with placebo, but did not show fistula healing when patients were treated for 10 weeks [27]. The authors found no evidence of efficacy in patients with abdominal fistulas. A more recent open study by González-Lama et al. [28], of 10 patients showed substantial healing, with 40% achieving complete clinical response and 50% achieving a partial response, but patients were treated for 6 to 24

months. Long-term therapy may, therefore, be required for achieving healing using this medication. Adverse events of tacrolimus therapy include headache, increased serum creatinine levels, insomnia, leg cramps, paresthesias and tremor, which could be managed with dose reduction. Methotrexate has been studied in CD patients with fistulas. In a small study in 16 patients, 4 (25%) had complete closure of fistulas and 5 (31%) a partial response [29]. Therefore, methotrexate should be tried, especially in patients not responding to azathioprine/6-mercaptopurine.

Anti-TNF Agents

In the first anti-TNF-alpha antibody trial for fistulizing CD, Present et al. [13] investigated 94 patients who received three infusions of infliximab therapy. Most patients had perianal fistulas. Sixty-eight percent of patients had a clinical response, with 55% closing all fistulas. The ACCENT 2 trial has extended these findings [17]. Of 306 actively treated patients, 64% had an initial response with 50% or more of fistulas closing. Of these initial responders treated with infliximab, 36% were healed at one year after regular infliximab treatment, compared with 19% treated with placebo after the initial response. A post hoc analysis was performed to determine the efficacy and safety of infliximab in women with rectovaginal fistulas [50]. After the first three infusions, 61 and 45% of rectovaginal fistulas were closed at week 10 and 14, respectively. Among responders, 72% of rectovaginal fistulas were no longer draining at week 14. The duration of rectovaginal closure was longer in the infliximab maintenance group (median 46 weeks) than in the placebo group (33 weeks). Side effects include increased risk of infections (including tuberculosis), malignancies and immunological reactions (infusion reactions, delayed hypersensitivity reactions), and in rare cases drug-induced lupus after exposure to infliximab. In two multicenter trials evaluating infliximab for induction and maintenance [13, 50] therapy for fistulizing CD, 11% and 15% developed abscesses related to their fistulae. Abscess formation likely occurred in these patients due to closure of the cutaneous opening of the fistula tract prior to the opening from the gastrointestinal tract. Adalimumab is a fully humanized antibody to TNF. In a recent large placebo-controlled Crohn's trial of adalimumab, 113 patients also had perianal fistulas. Two thirds of patients had one fistula whereas one third of patients had more than one fistula. Patients received adalimumab 80 mg initially, then 40 mg two weeks later, followed by 40 mg every two weeks, 40 mg weekly, or placebo. Patients with draining fistulas were evaluated for healing at week 26 and 56. Thirty percent (21 of 70) of all randomized patients on active adalimumab maintenance treatment had complete healing at both time points, compared with 13% (6 of 47) on placebo maintenance [32]. Adalimumab represents an option for patients who have lost response or who have become intolerant to infliximab. Certolizumab pegol is a humanized TNF antibody with a pegylated Fab fragment. This compound has been evaluated in two large studies (PRECiSE 1 and 2) in patients with CD [34, 35]. In those two studies, only a small number of included patients had a fistulizing disease and complete fistula healing was not statistically different between the placebo group and the certolizumab pegol treatment group. A small open-label study showed a reduction of >50% draining fistulas of 72% at week 6 [15].

Other Therapies

Another approach that has been described is treatment with an oral formulation of adsorptive carbon [AST-120 (Kremezin), Kureha Corp., Tokyo, Japan]. A placebo-controlled trial involving 62 patients with intractable anal fistulas due to CD found significantly higher rates of improvement (37 vs. 10%) and remission (30 vs. 7%) after eight weeks of treatment [36]. The drug, which is approved in Japan for treatment of chronic kidney disease, adsorbs some low-molecular weight substances such as uremic toxins. The authors hypothesized that intraluminal binding of some of these toxins may help to heal fistulas.

Surgical Management

The goal of surgical therapy is to eradicate the fistula while preserving fecal continence. The surgical approach depends upon the type of fistula. In patients with intersphincteric fistulas, the fistula tract can be laid open in the form of a primary fistulotomy. The base of the wound is then curetted and left open to heal by secondary intention. The traditional mainstay of fistula treatment has been drainage, and use of a non-dissolving thread (seton) inserted loosely through the fistula track to maintain patency. The seton can be removed when the track is healing or left in situ long term if healing is not occurring. This surgical approach prevents sphincter damage by prevent-

ing recurrent abscess formation. Up to 20–80% of CD patients with perianal fistulas will eventually require surgery [3] and about 30% of patients with complicated perianal CD may eventually require a permanent stoma [51, 52]. The presence of active proctitis reduces the chance of fistula healing and the proctitis needs to be treated aggressively if fistula healing is to be achieved [53]. In an intractable situation in which there is extensive perianal disease and seton drainage provides inadequate, the creation of a stoma, to divert the fecal stream away from the anal canal sometimes is considered. In one series this lead to early remission of anal disease in 81% of patients, but three quarters of these patients relapsed at a median of 2 years after stoma formation [54]. Another technique used for high trans-sphincteric fistulas is a partial fistulectomy and endoanal advancement flap. With this technique the fistula is cored out from the external opening up to the external circumference of the sphincter muscle. The remaining portion of the tract is then curetted and cleaned of any residual epithelial or granulation tissue. The internal opening is cauterized and curetted and then a proximal flap of mucosa is developed and slid over the internal opening. Usually the underlying rectal wall is also closed. Results with this procedure are varied but the technique allows for treatment of these high fistulas without division of the sphincter complex. A relatively new treatment for high trans-sphincteric or other complicated fistulas is injection of fibrin glue. The fibrin glue can be made ahead of time in the blood bank, or a commercial preparation is available. Early reports have described eradication of fistulas in up to 60% of patients with complex tracts [55–57]. However, recrudescence occurs commonly. One of the largest reports, for example, included 42 patients, most of whom had deep transsphincteric fistulas [58]. Durable healing was achieved in only 31% of patients. Nevertheless, the authors concluded that fibrin glue was still a reasonable option given its low morbidity and relative simplicity. Fibrin glue has also been used successfully in patients with anal fistulas related to CD [59]. Other adhesive products are also being developed [60].

Conclusion

Perianal fistulas lead to substantial physical and emotional distress because of pain, discharge, incontinence, perianal and genital disfigurement, and slow resolution even with treatment. With an expected spontaneous healing rate of only 10%, fistulizing CD requires a comprehensive strategy with a medical and possible surgical approach. Antibiotics are indicated and both ciprofloxacin and metronidazole are used in patients with fistulizing CD. Azathioprin/6-mercaptopurin or methotrexate should be given early in the disease. In the case of resistance or intolerance, infliximab should be initiated. Cyclosporin and tacrolimus should be tried in patients who fail to respond to infliximab. Synergistic strategies between medical physicians and surgeons are desperately needed and should be evaluated in controlled trials.

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