Research Review
EDUCATIONAL SERIES

Managing fistulising Crohn's Disease

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About this Review

This review is intended as an educational resource for health professionals. It discusses the incidence, diagnosis and treatment of fistulising Crohn's disease. Peer-reviewed clinical trial evidence on the use of biologic agents for the treatment of this condition is presented with accompanying expert commentary that is intended to inform readers about current research in this area.

About Research Review

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Fistula - a feared complication in Crohn's disease

Crohn's disease may be complicated by the formation of fistulas (abnormal passageways between the bowel and other structures) for which surgical intervention may be required. Fistulas may develop between two segments of bowel (enteroenteric fistula), between the bowel and the vagina (rectovaginal), between the bowel and the bladder (enterovesicular) or between the bowel and the skin (enterocutaneous). They are usually the consequence of an abscess that penetrates into surrounding tissue, consequently forming a fistulous tract.[1]

The development of fistulas is feared by both patient and clinician. It is estimated that 20-50% of individuals with Crohn's disease will develop this serious manifestation at some point during the course of their disease; the majority of patients will have one fistula episode over a 20-year period, while approximately one-third will experience two or more fistula episodes over such a time frame.[2-5] Estimates also indicate that 13-43% of individuals with Crohn's disease have involvement in the perianal region, and that fistula more frequently occur in patients with perianal involement, comprising half of all fistula cases.[5-8] A recent population-based cohort study conducted in Canterbury, New Zealand, revealed that 190 (26.6%) of 715 patients with Crohn's disease had symptomatic perianal disease, and 50% of those patients had fistulas (more than half were complex).[8] The study also revealed a cumulative probability at 20 years of experiencing a perianal fistula of 28.3%.[8] Studies in children suggest that approximately 10% of those newly diagnosed with Crohn's disease will have perianal fistulas and/or abscesses at the time of their diagnosis.[9]

Impact of fistulas on quality of life

Studies have consistently shown significant reduction in quality of life for patients with Crohn's disease.[10-12] Furthermore, as disease onset is most common during young adult years, lost productivity applies not only to work, but also to educational and social activities resulting in a detrimental effect on long-term personal and professional achievement.[13] Children with Crohn's disease not only have a more aggressive phenotype, but live with the illness for longer with consequent negative medical, nutritional and psychological impacts.[14] As one can imagine, life with Crohn's disease is further complicated by the presence of fistulas and their consequences such as perianal drainage, abscess formation, pain, dyschezia, dyspareunia and faecal incontinence; individuals with perianal fistulas are at an increased risk of developing faecal incontinence due to damage of the anal sphincter complex or from overly aggressive surgery. These symptoms can be extremely distressing and can further impair health-related quality of life.[15]

The economic burden of fistulising disease

It has been estimated that Crohn's disease costs New Zealand more than $58 million annually in healthcare expenditure, a significant proportion of which is associated with the treatment of fistulising disease. Recent research by Lion and colleagues investigating the costs associated with perianal Crohn's disease in patients in Christchurch, revealed a total one-year cost per patient of $20,366 (direct costs $18,261; indirect costs $2,105).[16] Extrapolating this data across New Zealand, these researchers estimated the cost of perianal Crohn's disease in one year to be $36.7 million. These findings are in line with those of a previous study revealing that the presence of fistulas in Crohn's disease almost doubles the direct medical costs related to the disease.

The Christchurch data revealed that expensive pharmaceuticals comprise a significant proportion of the direct costs associated with the disease, with biologics making up 61% of the pharmaceutical costs.[16] The greatest indirect cost associated with perianal disease was patient and immediate family absenteeism from work.

Diagnosing fistulas

Accurate characterisation of fistulising disease is critically important in order to ensure appropriate treatment. Investigations for perianal fistulas include MRI of the pelvis and rectum, examination under anaesthesia, and anal ultrasound. Imaging for non-perianal fistulas includes contrast imaging or CT/MRI. At the time of examination, the disease extent throughout the entire gastrointestinal tract should be ascertained; in more than 10% of patients, perianal fistulisation is the initial manifestation of Crohn's disease.[1,7,8]

In clinical practice, perianal fistulas are classified broadly as simple (low [below dentate line]; single external opening; not painful; not rectovaginal; no anorectal stricture) or complex (high [above dentate line]; multiple openings; evidence of abscess; possible pain; possibly rectovaginal; possible anorectal stricture or active rectal disease).[17]

Options for medical treatment

Fistulas rarely heal, with rates of spontaneous closure ranging from 6-13%.[18] While surgical resection is often effective, fistulas may recur at other sites. A decade ago the goal of treatment in fistulising disease was to improve drainage. Today, therapeutic goals are to close and maintain closure of the fistulas, to reduce the incidence of infection in those persisting and to reduce the need for surgical interventions.[1]

Options for medical treatment include antibiotics, immunomodulators and biologics (tumour necrosis factor [TNF]-α inhibitors). Most published studies focus on therapy for external fistula (i.e. perianal) and data on therapy for internal fistula are scarce. While 5-aminosalicylates and corticosteroids are sometimes used in the treatment of Crohn's disease, there is no role for them in the treatment of fistulising disease and in fact, corticosteroids have been shown to have a detrimental effect in fistula healing.[1]

Antibiotics

Antibiotics (most commonly metronidazole) are used as first-line treatment for the short-term management of fistulas and associated infections, but their use does not normally result in fistula healing and they are slow to work.[1] Metronidazole may need to be taken for 6-8 weeks before a response is seen and therapy is usually continued for 3-4 months.[1] Ciprofloxacin may also result in symptom improvement, but the long-term use of both of these antibiotics is associated with side effects.[1,7] Studies have also shown a high risk of relapse after these agents are stopped.[7] Combining antibiotics with azathioprine or 6-mercaptopurine may be beneficial.[1,7,19]

Immunosuppressive agents

A meta-analysis of five randomised clinical trials (with fistula closure as a secondary endpoint) showed azathioprine and 6-mercaptopurine to be effective in fistula closure (closure in 54% of azathioprine/6 mercaptopurine recipients vs 21% of placebo recipients; odds ratio 4.4; 95% CI 1.5-13.2).[20] Intravenous cyclosporin and oral tacrolimus have both been shown in small studies to improve or heal some patients short-term, but they often relapse on stopping the drug.[1] A small study of methotrexate use in Crohn's patients with fistulas showed a 25% complete closure rate and a 31% partial response rate, and another study revealed a fistula improvement rate of 44%, suggesting that this agent should be considered for treatment, especially in patients not responding to azathioprine or 6-mercaptopurine.[1,21,22]

Biologics

The use of infliximab to heal fistulising Crohn's disease was established by Present et al in 1999 (68% response and 55% closure of all fistulas compared with 26% for placebo) and its efficacy as maintenance therapy was shown in the ACCENT II study.[23, 24] Sustained complete clinical response with the agent was evident up to 1 year in 36% of cases compared with 19% of controls and the median time to loss of response was prolonged from 14 to 40 weeks.[24]

The efficacy of adalimumab in fistulising Crohn's disease was demonstrated in the CHARM trial, with complete fistula closure at week 26 in 30% of those treated versus 13% of controls and at week 56 in 33% versus 13% of controls; 90% maintained fistula healing following 1 year of adalimumab maintenance therapy.[25,26] Furthermore, a prospective study by Ng et al revealed that infliximab/adalimumab improves Health-Related Quality of Life at 12 months in patients with Crohn's related perianal fistulas and that this improvement is most pronounced in those with clinical and MRI healing.[15]

Both infliximab [Remicade®] and adalimumab [Humira®] are registered for use in New Zealand for the treatment Crohn's disease. Infliximab is indicated for the treatment of draining enterocutaneous fistulas in adults with fistulising disease and is fully funded.

Other agents

Granulocyte-macrophage colony-stimulating factor, charcoal, parenteral nutrition, mycophenolate, thalidomide and hyperbaric oxygen have all been used in the treatment of Crohn's disease, but there are no specific studies examining the use of these medications for the treatment of fistulising Crohn's disease.[7] Early studies have shown evidence for the efficacy of intrafistular injections of autologous bone marrow-derived mesenchymal stromal cells in the healing of fistulas in Crohn's disease.[27]

Treatment guidelines

Current best practice recommends aggressive medical therapy with biological agents in combination with surgical investigation and treatment in order to optimise clinical success and minimise patient suffering and tissue damage due to inadequately controlled disease.[28] The World Congress of Gastroenterology on Biological Therapy for IBD (inflammatory bowel disease), along with the European Crohn's and Colitis Organization states that a complex fistula in Crohn's disease is an indication for biological therapy (infliximab) in conjunction with surgical drainage and possibly ciprofloxacin.[28]

After reviewing international guidelines and considering local limitations, the New Zealand Society of Gastroenterology developed local guidelines in order to support gastroenterologists in their decision making regarding the use of biologic agents in IBD.[29] For the treatment of fistulising and perianal disease, the New Zealand guidelines recommend an initial perineal MRI or endoanal ultrasound in order to define the extent of disease and to exclude drainable collections. They recommend draining sepsis, placement of Seton sutures (devices to keep fistulas open to allow drainage), treatment with appropriate antibiotics and the optimisation of standard immunomodulator therapy (especially with thiopurines – measuring 6-thioguanine [6-TGN] levels). For patients who have failed antibiotics and/or immunomodulators, then infliximab should be used along with perianal surgery in order to eliminate sepsis; the standard induction regimen for infliximab involves three IV infusions of 5 mg/kg administered at weeks 0, 2 and 6. Maintenance of healing may be achieved with infliximab or adalimumab, but while both agents have been shown to be effective at maintaining closure neither are funded in New Zealand for this indication.

EXPERT COMMENTARY ON KEY BIOLOGICAL THERAPY STUDIES

Infliximab for the treatment of fistulas in patients with Crohn's disease[23]

Authors: Present DH et al

Summary: The efficacy of infliximab for the treatment of fistulas in adult patients with Crohn's disease was examined in this randomised, multicentre, double-blind, placebo-controlled trial involving 94 individuals randomly assigned to receive one of three IV regimens administered at weeks 0, 2 and 6: placebo (n = 31); infliximab 5 mg/kg (n = 31); infliximab 10 mg/kg (n = 32). All patients had draining abdominal or perianal fistulas for at least 3 months. The primary endpoint of reduction of 50% or more from baseline in the number of draining fistulas observed at two or more consecutive visits was achieved by significantly more infliximab 5 mg/kg recipients and infliximab 10 mg/kg recipients than placebo recipients (68% and 56% vs 26%; p = 0.002 and p = 0.02, respectively); response rates in the two infliximab groups were not significantly different. A secondary endpoint of closure of all fistulas was achieved by significantly more infliximab 5 mg/kg recipients and infliximab 10 mg/kg recipients than placebo recipients (55% and 38% vs 13%; p = 0.001 and p = 0.04, respectively). Fistulas remained closed in all groups for a median of 3 months.

Comment: This landmark study moved the goal posts with regard to optimal treatment outcomes for perianal fistulae in patients with Crohn's disease. Complete and clinically significant healing were unattainable for most patients with fistulising perianal Crohn's disease, but this paper showed that such outcomes were attainable. This paper demonstrated that high induction rates were possible amongst this group of patients. Furthermore, the similar efficacy rates of both 5 mg/kg and 10 mg/kg helped to define infliximab doses to be used in future studies. One of the major concerns raised from this trial was the recurrence of fistulae after the cessation of infliximab. However, long-term response rates were to follow in the ACCENT II study.

Findings from the ACCENT II study

Infliximab maintenance therapy for fistulizing Crohn's disease[24]

Authors: Sands BE et al

Summary: The multicentre, randomised controlled, double-blind ACCENT II trial (A Crohn's Disease Clinical Trial Evaluating Infliximab in a New Long-term Treatment Regimen in Patients With Fistulizing Crohn's Disease) involved 306 adult patients with Crohn's disease who had single or multiple draining fistulas for ≥3 months and who received induction with an IV infusion of infliximab 5 mg/kg at weeks 0, 2 and 6. The trial investigated the efficacy and safety of maintenance infliximab in a total of 195 patients who had exhibited a response to the agent (defined as a reduction of ≥50% from baseline in the number of draining fistulas at 10 and 14 weeks) and in 87 patients who had no response. Patients were then randomly assigned to receive either infliximab 5 mg/kg (responders n = 96; non-responders n = 43) or placebo (responders n = 99; non-responders n = 44) every 8 weeks, up to week 46. Patients were followed until week 54 and were assessed for loss of response, defined as recrudescence of fistulas, the need for a change or addition to Crohn's disease therapy for persistent or worsening luminal disease, the need for surgical intervention, or the discontinuation of study medication due to a perceived lack of efficacy. For responders, the time to loss of response was significantly longer for infliximab recipients than placebo recipients (median >40 weeks vs 14 weeks; $p < 0.001$). Furthermore, at week 54, significantly more infliximab recipients exhibited a complete response (absence of draining fistulas) to therapy than placebo recipients (36% vs 19%; $p < 0.009$). Among patients who lost their response, 25 out of 41 (61%) patients who crossed over from placebo maintenance to infliximab 5 mg/kg experienced reestablishment of a response. This phenomenon was also seen in 12 out of 21 (57%) patients who crossed over from infliximab 5 mg/kg to infliximab 10 mg/kg following loss of response. Among the 44 patients who had no response at the time of randomisation and subsequently received placebo, seven (16%) exhibited a response, while nine (21%) of the 43 patients who subsequently received infliximab had such a response (this difference was not significant). Patients with fistulas appeared to tolerate infliximab maintenance therapy well.

Comment: While the study by Present et al was groundbreaking in showing the potential for healing perianal fistulae in patients with Crohn's disease, gastroenterologists recognised that short-term healing was of little consequence if the effects cannot be maintained. Crohn's disease is a lifelong disease and maintenance of remission remains our therapeutic goal (in the absence of a known cure at this point). ACCENT II showed that complete response can be maintained in almost half of patients who initially respond to infliximab and, furthermore, those who crossed over from placebo to infliximab were also able to maintain remission. While not all patients achieved a complete response, the high rates were significantly better than seen for more conventional agents.

Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study[30]

Authors: Sands BE et al

Summary: This post-hoc analysis of the ACCENT II study was undertaken to determine the efficacy and safety of infliximab in women with rectovaginal fistulas. Out of a total of 138 women in the study, 25 (18.1%) had at least one draining rectovaginal fistula at baseline (two women had two fistulas). Following induction with an IV infusion of infliximab 5 mg/kg at weeks 0, 2 and 6, 60.7% of rectovaginal fistulas were closed at week 10 and 44.8% were closed at week 14. Among those who had responded to induction therapy, 13 out of 18 (72.2%) rectovaginal fistulas had closed at week 14. Fistulas remained closed longer in responders in the infliximab maintenance group than in responders randomised to placebo maintenance (median of 46 weeks vs 33 weeks).

Comment: Rectovaginal fistulae are amongst the most devastating complications of Crohn's disease. They are associated with an enormous reduction in quality of life and will often result in the need for colectomy and end ileostomy with the associated risks of pelvic surgery. There were few data showing efficacy for medical therapies until this post-hoc analysis of the ACCENT II data. This study confirmed that the efficacy of infliximab for perianal fistulae could be extended to women with rectovaginal fistulae.

Maintenance infliximab does not result in increased abscess development in fistulizing Crohn's disease: results from the ACCENT II study[31]

Authors: Sands BE et al

Summary: Data from the ACCENT II study were analysed in order to assess whether infliximab exposure has an influence on fistula-related abscess development. All patients received infliximab during the induction phase of the study and infliximab exposure in the infliximab maintenance group was approximately two-fold higher than in the placebo maintenance group. In total, 21 (15%) patients in the infliximab maintenance group and 27 (19%) patients in the placebo maintenance group had at least one newly developed fistula-related abscess; this difference was not significant. Furthermore, the number of fistula-related abscesses diagnosed over time did not differ between the two groups.

Comment: While infliximab was efficacious, at healing fistulae, was it at the expense of developing abscesses? Theoretically if a fistula closes then there may be an increased risk of abscess formation in the fistula tract. This post-hoc analysis did not demonstrate an increased risk of this complication in those treated with infliximab compared to those receiving placebo.

Infliximab maintenance treatment reduces hospitalisations, surgeries, and procedures in fistulising Crohn's disease[32]

Authors: Lichtenstein GR et al

Summary: The effect of infliximab maintenance therapy on hospitalisations, surgeries and procedures in patients with fistulising Crohn's disease enrolled in the ACCENT II study was examined. Compared with infliximab induction responders who had been randomised to placebo maintenance (n = 99), responders to infliximab induction therapy who had been randomised to infliximab maintenance therapy (n = 96), experienced significantly fewer hospitalisation days (0.5 vs 2.5 days; $p < 0.05$), lower mean numbers of hospitalisations (11 vs 31; $p < 0.05$), fewer surgeries and procedures (65 vs 126; $p < 0.05$), fewer inpatient surgeries and procedures (7 vs 41; $p < 0.01$) and fewer major surgeries (2 vs 11; $p < 0.05$).

Comment: Generally improving a patient's health and reducing symptoms leads to a reduction in health care utilisation. However, increasingly we need to demonstrate this, particularly to justify the costs of new pharmaceuticals. This ACCENT II analysis demonstrated major reduction in hospitalisations, minor and major surgeries. This analysis is important because the cost savings associated with fistula healing are seen in non-pharmacological areas. Those who decide on funding of new pharmaceuticals need to look widely for the direct cost savings across the health sector.

Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial[25]

Authors: Colombel JF et al

Summary: The randomised, double-blind, placebo-controlled, multicentre CHARM (Crohn's Trial of the Fully Human Antibody Adalimumab for Remission Maintenance) trial evaluated the efficacy and safety of SC adalimumab in the maintenance of response and remission in adults with moderate-to-severe Crohn's disease. A total of 854 patients were enrolled in the trial and received open-label induction therapy with SC adalimumab 80mg (week 0) followed by 40mg at week 2. Patients were stratified by response (decrease in the Crohn's Disease Activity Index [CDAI] ≥70 points from baseline) at week 4 and 778 patients were randomised to one of three treatment regimens through week 56; placebo (170 responders and 91 non-responders); adalimumab 40mg every other week (eow; 172 responders and 88 non-responders); adalimumab 40mg weekly (157 responders and 100 non-responders). At weeks 26 and 56, the percentage of week-4 randomised responders in clinical remission (CDAI score <150) was significantly greater in the adalimumab 40mg eow and 40mg weekly groups versus placebo: 40% and 47% vs 17% ($p < 0.001$); 36% and 41% vs 12% ($p < 0.001$), respectively. With regard to fistulas, at both weeks 26 and 56, complete closure of fistulas that were draining at screening and baseline visits (n = 117) was achieved in a greater percentage of adalimumab 40mg eow and adalimumab 40mg weekly recipients compared with placebo recipients; 33% (10/30) and 28% (11/40) vs 13% (6/47; $p = 0.043$ for combined adalimumab dosing groups vs placebo), and 37% (11/30) and 30% (12/40) vs 13% (6/47; $p = 0.016$ for combined adalimumab dosing groups vs placebo), respectively. All of the patients with complete fistula closure at week 26 continued to have complete fistula closure at week 56. Adalimumab was well tolerated and safety findings revealed significantly ($p < 0.05$) more patients receiving placebo discontinuing treatment due to an adverse event than those receiving adalimumab; 13.4% vs 6.9% (40mg eow group) and 4.7% (40mg weekly group).

Comment: Adalimumab was the second anti-TNF agent to become available for the treatment of Crohn's disease. In order to achieve registration across a number of related Crohn's disease indications, a very large study (by IBD standards) was completed. Combining efficacy data from the 40mg weekly and eow groups showed that adalimumab was superior to placebo for healing fistulae. While the efficacy of adalimumab 40mg eow was not established in this study, this dosage is routinely used to treat patients with perianal Crohn's disease, and open label studies and case series support this approach.

Adalimumab for the treatment of fistulas in patients with Crohn's disease[26]

Authors: Colombel JF et al

Summary: The ADHERE (Additional Long-Term Dosing with HUMIRA to Evaluate Sustained Remission and Efficacy in Crohn's disease) trial, an extension of the CHARM trial, evaluated the 2-year maintenance of fistula healing during treatment with adalimumab. Of those patients with healed fistulas at week 56 of the CHARM trial who completed the 1-year ADHERE extension trial (n = 31) 90% maintained fistula healing following 1 year of open-label adalimumab therapy (40mg weekly or eow).

Comment: Adalimumab has shown in all long-term studies of Crohn's disease that if one responds initially, one is likely to continue to do so. The sustained complete remission rates of 90% in those who healed fistulae shows excellent long-term results of these agents. As mentioned earlier, Crohn's disease is a long-term illness and long-term solutions need to be found to control symptoms. These data help to show longer-term efficacy. The next question will be when one can hope to stop the drug.

Concluding remarks

Perianal fistulae are a common but disabling complication of Crohn's disease that are associated with reduced quality of life, increased rates of hospitalisation, surgery and often colectomy. The management of perianal Crohn's disease requires close collaboration with colorectal surgeons in order to ensure that sepsis is drained. Antibiotics play an important role in this short-term goal. Medical therapies have been disappointing with standard immunomodulators such as the thiopurines and methotrexate having modest results at best. The anti-TNF drugs offer significantly improved outcomes for these patients although not all will respond. Those who do respond may heal their fistulae although the optimal duration of treatment remains unknown.

While anti-TNF drugs are funded in New Zealand, the use of these drugs for perianal disease remains inconsistent throughout the country. Infliximab is fully funded and indicated for fistulising Crohn's disease, but access varies widely between district health boards. While the evidence for the efficacy of adalimumab for fistulising perianal Crohn's disease is less compelling than for infliximab, long-term results show that patients who respond can do very well in the long term. However, Pharmac has not provided reimbursement for adalimumab for the indication of perianal Crohn's disease. Improved and equitable access to anti-TNF drugs for the treatment of fistulising perianal Crohn's Disease is desperately needed.

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