

Management of perianal Crohn's disease

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P Rutgeerts. Management of perianal Crohn's disease. *Can J Gastroenterol* 2000;14(Suppl C):7C-12C. Perianal inflammation is a disabling manifestation of Crohn's disease. The primary lesions found in perianal Crohn's disease evolve in parallel with the disease elsewhere in the bowel. Although the spontaneous resolution of anal lesions is observed in up to half of patients, the penetrating nature of the disease may lead to secondary lesions including complex fistulae. In some patients, this, in turn, results in the gradual destruction of the sphincter apparatus and anal incontinence. These patients, after years of suffering, often require proctectomy. Control of activity, overall, is the first step in the management of perianal Crohn's disease. Sepsis should be controlled by the drainage of abscesses and by long term use of setons. Although antibiotics and standard immunosuppression often improve perianal fistulae, their action is usually slow and incomplete. Management of perianal Crohn's disease has changed thoroughly in the past two years since the introduction of monoclonal antibodies to tumour necrosis factor (infliximab). Complete arrest of the drainage of fistulae was obtained in 46% of patients after the administration of 5 to 10 mg/kg of infliximab at weeks 0, 2 and 6, with a median duration of effect of 12 weeks. In these patients, long term management of their bowel disease will likely require the repeated use of infliximab. Studies to evaluate this are underway.

Key Words: *Crohn's disease; Fistula; Infliximab; Monoclonal antibodies; Perianal Crohn's disease*

Traitement de la maladie de Crohn périanale

RÉSUMÉ : L'inflammation périanale est une manifestation débilitante de la maladie de Crohn. Les lésions primaires observées dans la maladie de Crohn périanale suivent une évolution parallèle à celles sises dans d'autres parties de l'intestin. Même si on observe une guérison spontanée des lésions anales jusqu'à dans la moitié des cas, la nature envahissante de la maladie peut entraîner des lésions secondaires, par exemple des fistules complexes. Chez certains patients, ces fistules complexes provoquent à leur tour la destruction progressive du sphincter anal, d'où incontinence anale. Ces patients, après des années de souffrance, doivent souvent subir une proctectomie. La limitation de l'activité, en général, constitue la première étape du traitement de la maladie de Crohn périanale. Le drainage des abcès et l'utilisation à long terme de sétons permettent d'éviter les septicémies. Même si les antibiotiques et les immunosuppresseurs usuels améliorent souvent l'état des fistules périanales, leur action est généralement lente et incomplète. Le traitement de la maladie de Crohn périanale a connu un changement en profondeur au cours des deux dernières années, depuis l'arrivée des anticorps monoclonaux contre le facteur de nécrose des tumeurs (infliximab). En effet, l'administration d'infliximab à raison de 5 à 10 mg/kg aux semaines 0, 2 et 6 a rendu possible l'arrêt complet du drainage des fistules chez 46 % des patients, et la durée médiane de l'effet a été de 12 semaines. Toutefois, le traitement à long terme de la maladie, chez ces patients, nécessitera sans doute l'administration répétée d'infliximab. Des études en cours évaluent cet aspect.

BACKGROUND

Although the original description of Crohn's disease did not include the mention of anal lesions (1), these were reported by Bissell (2) shortly afterwards. Subsequently, Morson and Lockhart-Mummery (3) from St Mark's Hospital in London described the sarcoid-like histological lesions.

Morson and Lockhart-Mummery (3,4) also studied the prognosis of similar histological lesions found in the biopsies

of fissures and fistulae in patients not diagnosed with Crohn's disease. Approximately half of these patients with sarcoid-like lesions developed intestinal Crohn's lesions a few months to more than 10 years after anal surgery. It was not until the paper by Gray et al (5) that the full clinical spectrum of anal Crohn's disease was described.

Because there is no uniformity in the description of the lesions, it is not surprising that the reported incidence of

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perianal lesions in Crohn's disease varies from 25% to 80%. Perianal lesions, and especially primary Crohn's fissures, develop in an area of aggregation of lymphoid tissue around the anal gland ducts. Crohn's disease often occurs in areas of the bowel where slow transit of fecal material occurs. The narrow anal canal favours passage of liquid feces into the anal glands, where an interaction with local lymphoid tissue leads to anal Crohn's lesions.

The lesions of perianal Crohn's disease can be classified as primary, secondary or incidental. Primary lesions are the consequence of the same idiopathic inflammatory process seen in the intestine. According to Hughes and Taylor (6), the same basic lesions, superficial ulcers, cavitating ulcers (perforating-type disease) and lymphedema, are present both in the bowel and at the anus. Extensive aggressive ulceration is specific to the anal region, and can involve the anal canal and skin, the vulva and the lower vagina. Secondary lesions arise due to mechanical and infective complications of the primary inflammatory lesions. Their evolution can best be understood based on local anatomy and the routes of spread of local infections. Incidental lesions such as hemorrhoids are not directly related to Crohn's disease.

Primary lesions: Primary lesions reflect the overall activity of Crohn's disease. They usually flare when the proximal bowel inflammation is active, and improve when bowel inflammation regresses. Primary lesions include Crohn's fissures, which resemble longitudinal ulcers, and an ulcerated external pile complex resulting from extensive lymphedema of the subcutaneous tissue. Particularly aggressive anal Crohn's disease is associated with cavitating ulcers at the dentate line and extensive aggressive erosive ulceration, extending to the vagina in women.

Secondary lesions: Primary Crohn's fissures may progress to subcutaneous fistulae, while the ulcerated pile complex leads to large anal skin tags. It is the cavitating ulcer that leads to deep abscesses and fistulae with complicated tracks and supra-sphincteric extension; the deep abscesses and fistulae heal poorly, if at all, because of fecal contamination. Anterior cavitating ulcers perforate directly into the vulva or the vagina, or extend up through the rectovaginal septum.

Anal strictures are not frequent. There may be a tight fibrotic stricture at the anorectal junction or an extensive dense perirectal stricture 2 or 3 cm above the anal canal, often accompanied by extensive perianal edema with extensive piles.

Prognosis of perianal lesions in Crohn's disease: Approximately half of the fissures and intrasphincteric fistulae in Crohn's disease heal spontaneously or after primary fistulotomy with control of intestinal disease. The prognosis of fistulae associated with cavitating ulcers above the anal sphincter, however, is gloomy. Complicated fistulae arise, giving rise to severe morbidity due to sepsis, as well as sphincter destruction and anal incontinence. Rectal excision is often unavoidable but greatly improves the quality of life in these patients. Anal fistulae in association with active rectal disease carry a poor prognosis. Fistulae associated with rectal disease are resistant to conservative surgery and will not improve un-

til activity of distal colonic disease is controlled (7). The outcome of perianal Crohn's disease is better in patients with small intestinal involvement.

Diagnosis and assessment of perianal Crohn's disease: In the presence of complex perianal Crohn's disease, examination under general anesthesia by an experienced proctological surgeon is the key assessment (8). Fistulograms are of limited value. Endoscopic ultrasonography may be helpful, but its accuracy is very operator dependent.

Magnetic resonance imaging can be very useful in Crohn's disease because it offers very good definition of the intersphincteric plane, the puborectalis sling, and elements of the pelvic floor and perirectal tissues (9). In Crohn's disease, it is frequently difficult to use endorectal coils because of the severity of the lesions. The same limitation exists for endorectal ultrasound. Most abscesses are detected by clinical examination and endoscopic ultrasonography, although magnetic resonance imaging is useful to identify proximal extension of abscesses and horseshoe fistulae with a supralelevator component. Magnetic resonance imaging should be used in the presence of unexplained sepsis in patients with perianal Crohn's involvement. At the current time, there does not seem to be an indication for its routine use, because of its cost and its limited added benefit in most cases.

Therapy for perianal Crohn's disease: The treatment of primary perianal Crohn's lesions is basically the same as for active Crohn's disease in the bowel. Sulphasalazine or 5-aminosalicylic acid (5-ASA) formulations have no role, but glucocorticosteroids may improve perianal inflammatory lesions in parallel with bowel inflammation. Local injection of a long-acting glucocorticosteroid formulation in the sphincter area may relieve pain from ulcerating perianal and anal canal disease (10). Glucocorticosteroid suppositories and enemas frequently improve concomitant rectal inflammation. Suppositories of beclomethasone dipropionate (3 mg) are particularly useful because of this agent's rapid metabolism and low systemic side effects from its high first pass effect.

Antibiotics are very useful adjunctive therapy and help in the control of local infections. The combination of ciprofloxacin 250 mg bid and metronidazole 500 mg bid is generally used.

The author has observed dramatic improvement of primary anal lesions in patients treated with infliximab for refractory bowel disease, but no prospective data are available. Control of Crohn's inflammation, with the healing of primary lesions, is the mechanism of action of infliximab, and healing of fistulae may result from that action.

TREATMENT OF PERIANAL FISTULIZING DISEASE IN CROHN'S DISEASE

If abscesses are present, they need to be drained: fistulous tracks need long term drainage using setons. Simple intersphincteric fistulae can be treated with primary fistulotomy after the control of active disease is achieved. Even the slightest disruption of the anal sphincter needs to be avoided

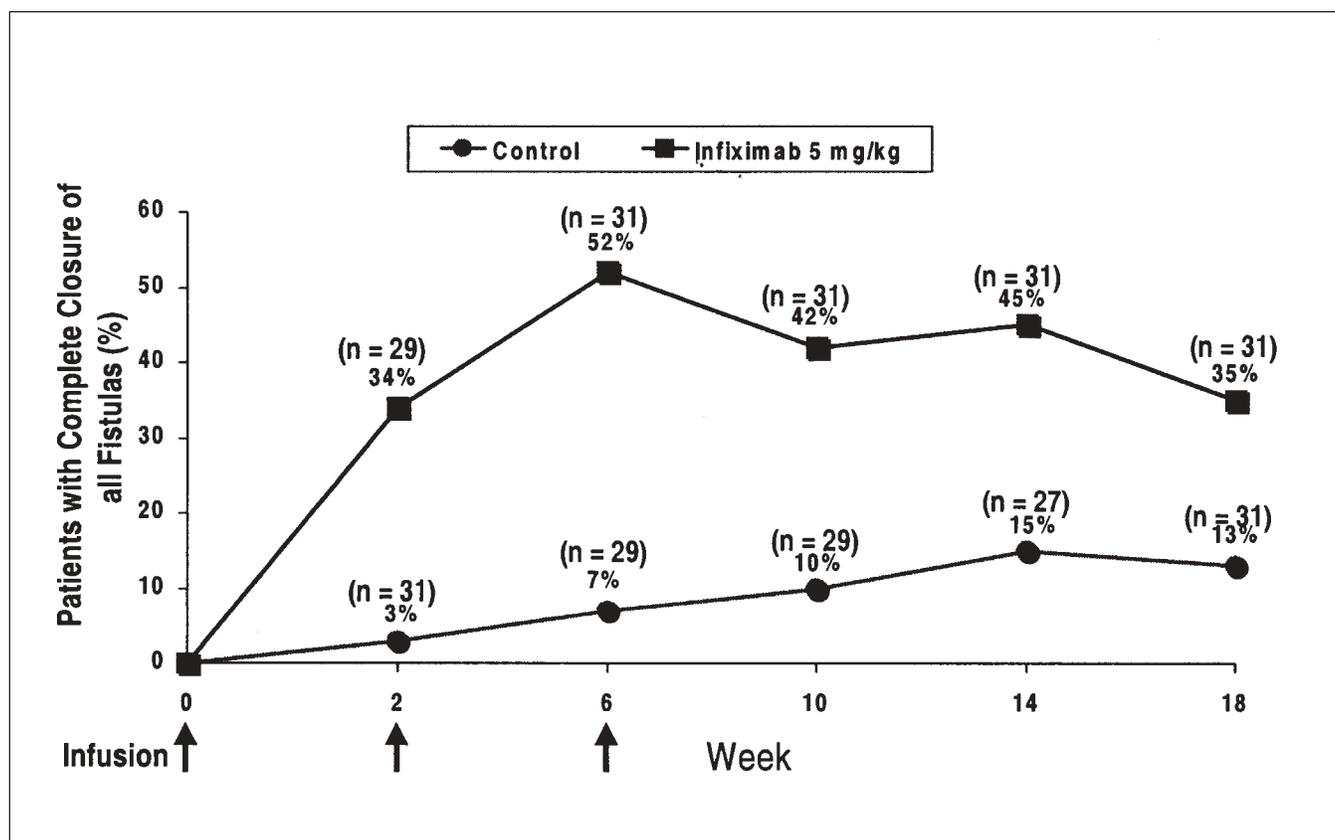


Figure 1) Rate of complete closure of all fistulae with infliximab

because incontinence may occur in the presence of diarrhea. Medical therapy of fistulizing perianal Crohn's disease involves the use of antibiotics, immunosuppressives and infliximab.

Antibiotics in the treatment of perianal Crohn's disease:

Only limited, uncontrolled data, with poorly defined endpoints, have been reported for the treatment of Crohn's disease with antibiotics. Bernstein et al (11) reported a study of 21 patients treated with high dosage metronidazole (20 mg/kg/day) and reported complete healing in 48% of patients, with advanced healing in a further 24%. On follow-up, a decrease in drug dosage resulted in the exacerbation of disease activity in all patients (12), with renewed control following dosage increases. In only 28% of the patients could the drug be successfully discontinued.

Jakovovits and Schuster (13) reported the effect of metronidazole (1000 to 1500 mg/day) in eight patients with Crohn's disease and perianal fistulae. Complete resolution of all symptoms occurred in 50% of the patients, and the effect was maintained after the cessation of therapy. In another uncontrolled trial, the combination of ciprofloxacin and metronidazole was effective in severe perianal Crohn's disease (14).

Immunosuppression for perianal fistulizing Crohn's disease – Cyclosporine: While intravenous cyclosporine is effective in the treatment of severe extensive ulcerative colitis, low dose oral therapy is not efficacious in Crohn's disease. Intravenous cyclosporine was reported useful in treating peri-

anal Crohn's disease in two studies. Hanauer and Smith (15) reported complete resolution of drainage from 10 of 12 fistulae after a mean of 7.9 days (range three to 28) in five patients, with two relapses under oral therapy. In the series of Present and Lichtiger (16), 14 of 16 patients (88%) responded to intravenous cyclosporine (closure 44%, improvement 44%). When switched to oral therapy, five patients relapsed. Egan et al (17) reported a partial response in seven of nine patients, with a relapse in five after discontinuation. These promising results were not confirmed in a Canadian study in children (18).

Azathioprine and 6-mercaptopurine: There are no randomized, controlled studies on the effect of azathioprine or 6-mercaptopurine (6-MP) for perianal fistulizing Crohn's disease. A subanalysis of the trial by Present et al (19) in refractory Crohn's disease examined 29 patients with perianal fistulae; 24% of patients had a partial response and 31% a complete response. The mean time to response was 3.1 months, and a maximal response was observed at eight months. A follow-up analysis in 34 patients by the same group revealed a partial response in 26% of patients and a complete response in 39%. Another study found very comparable results in 26 patients, with 54% displaying a partial response and 31% a complete response (20).

Infliximab for fistulizing Crohn's disease: A new development in the management of fistulizing Crohn's disease is use of the monoclonal chimeric antitumour necrosis factor anti-

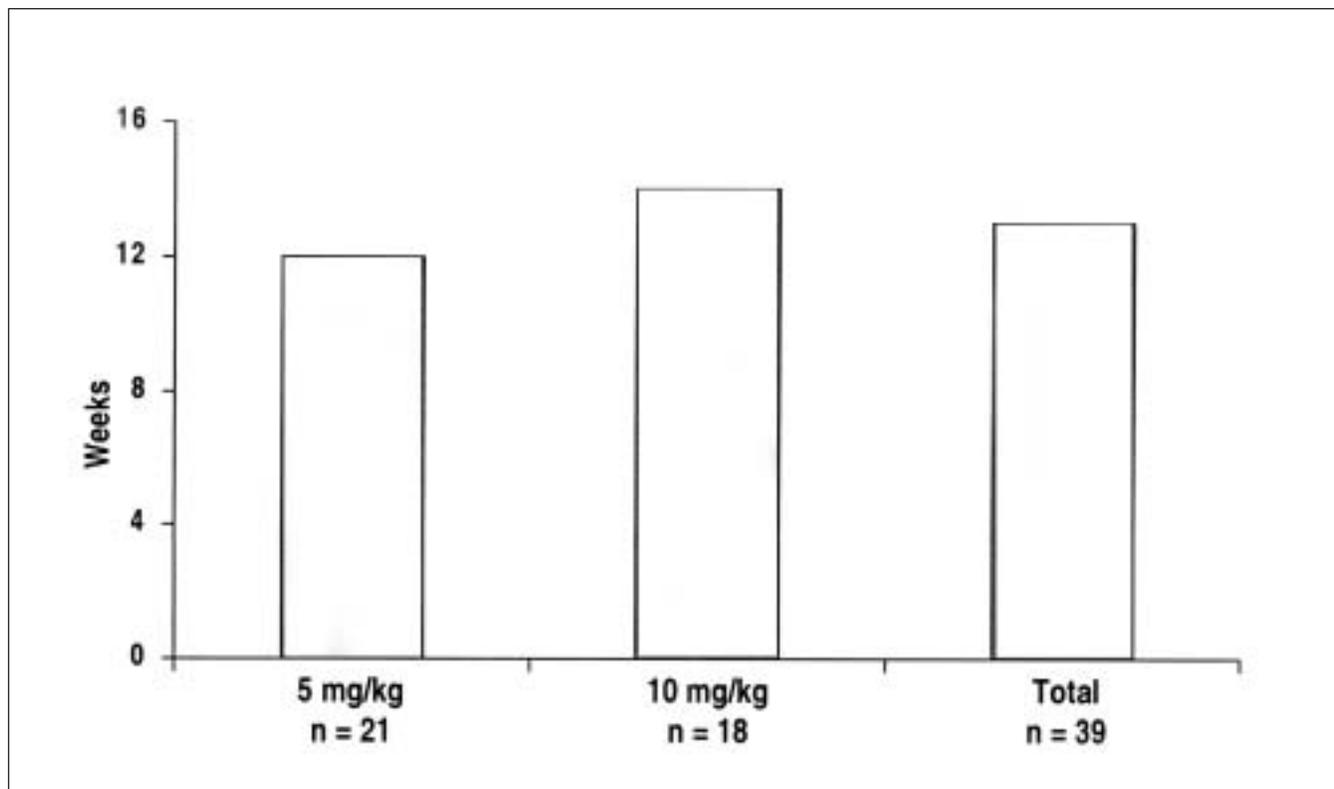


Figure 2) Duration of fistula closure: Median and interquartile range. Data on file, Centocor Inc, USA

bodies, infliximab (REMICADE, Centocor, USA). Infliximab works much more quickly than azathioprine. A complete response is achieved in 34% of patients at two weeks and in 52% at four weeks, after which the response rate plateaus (Figure 1).

In a pivotal study, Present et al (21) examined two infliximab dosages, 5 mg/kg and 10 mg/kg, given in three infusions at weeks 0, 2 and 6, and compared the effect with placebo. The primary efficacy endpoint was a 50% or greater reduction from baseline in the number of draining fistulae for at least two consecutive evaluation visits (at least one month apart). A fistula was considered closed if it was no longer draining despite gentle compression. Efficacy response variables were evaluated at weeks 2, 6, 10, 14 and 18. Secondary efficacy endpoints included the rate of complete response (closure of all fistulae for at least two consecutive study visits), Crohn's Disease Assessment Index score, patients' global assessment and quality of life measurements. The treatment was considered a failure if the patient required an increase in the dosage of their concomitant medication(s), initiation of additional medication(s) or surgery to treat the fistulae during the trial.

Patient demographic characteristics and baseline disease characteristics (disease duration and concomitant medications) were similar for all treatment groups. Study results showed that both infliximab treatment groups (5 mg/kg and 10 mg/kg) had a statistically significant, greater number of patients (39 of 63, 62%) achieving the primary endpoint

compared with the control group (eight of 31, 26%), $P=0.002$). Of patients receiving 5 mg/kg infliximab, 68% (21 of 31) achieved a 50% or greater reduction in the number of open fistulae compared with 26% of control patients (eight of 31, $P=0.002$). No dose-response effect was observed between the two infliximab treatment groups, although the 5 mg/kg dosage was at least as effective as 10 mg/kg.

The secondary endpoint of complete closure of all fistulae was seen in 46% (55% for 5 mg/kg infliximab; 38% for 10 mg/kg infliximab) of all infliximab-treated patients compared with 13% of the placebo-treated patients ($P=0.001$). Closure of draining fistulae by infliximab treatment was characterized by rapid onset (usually within two weeks) and a lasting benefit of action, with a median duration of closure of 12 weeks (Figure 2). After 22 weeks, there was no difference between either dose of infliximab and placebo in the proportion of patients responding. Patients with one draining fistula did as well as those with multiple draining fistulae. There was no difference in response or remission according to the concurrent medications.

The outcome of perianal Crohn's disease using infliximab therapy is comparable with the results in refractory intestinal Crohn's disease (22). Further studies (Accent II trial) will show whether repeated therapy allows the maintenance of the effect in the long term, as has been demonstrated for refractory disease (23).

Algorithm for treatment of perianal fistulizing Crohn's disease: The introduction of infliximab has dramatically

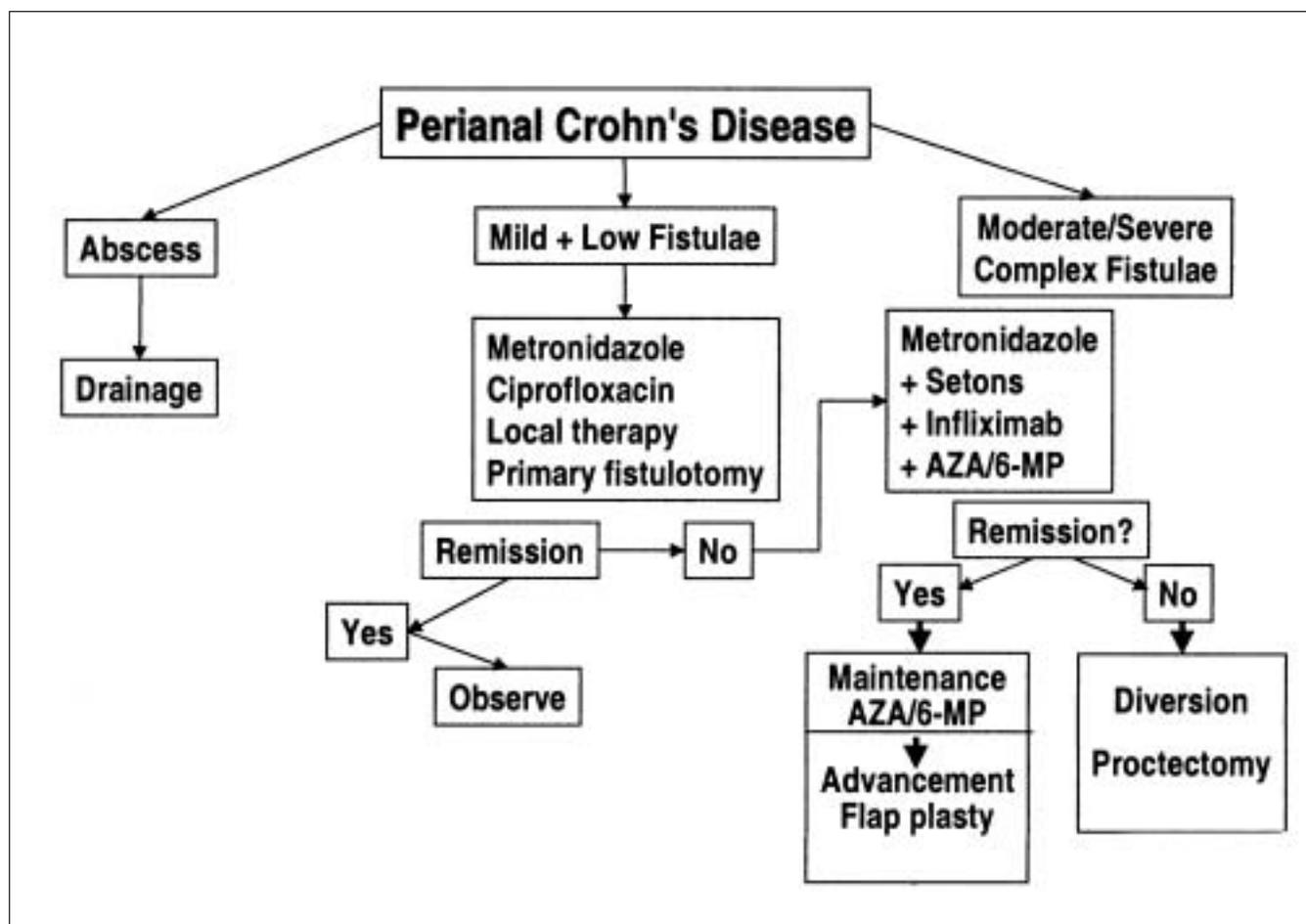


Figure 3) An algorithm for the management of perianal Crohn's disease. AZA/6-MP Azathioprine/6-mercaptopurine

changed the management of perianal Crohn's disease. The author proposes an algorithm built on the current evidence in Figure 3.

Infliximab as an adjunct to surgical therapy of perianal Crohn's disease: Suprasphincteric and rectovaginal fistulae can be treated with fistulotomy and sphincter repair after long term drainage, but the results in Crohn's disease are disappointing. Slow healing, sepsis and Crohn's relapse are frequent consequences, often resulting in incontinence. These fistula tracks can also be closed using transanal advancement flap plasty. A flap is raised from the dentate line including mucosa, submucosa and some circular muscle fibres. The fistula track is cored out and closed. The flap is then brought down to cover the defect. The vaginal or anal side of the fistula is left open for drainage.

The best results are obtained when this procedure is carried out with temporary defunctioning colostomy and control of Crohn's inflammation using immunosuppression. Exclusion criteria for transanal advancement flap plasty are active proctitis, undrained sepsis, large fistulae (greater than 3 cm) or recent fistulae (only a few weeks old). Long term success rates of up to 66% at three years have been described with this surgical approach.

CONCLUSIONS

The use of chimeric antitumour necrosis factor monoclonal antibody, infliximab, is an important step forward in the treatment of perianal Crohn's disease. Early use might allow control of the primary lesions of the anal canal and distal rectum, and prevent the occurrence of secondary complications including complex fistulae. In the presence of complicated disease, repeated administration of the drug may allow long term control of the disease.

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