Management of fistulas in patients with Crohn’s disease: Antibiotic to antibody

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Fistulization is a common complication of Crohn’s disease. The clinical significance of a fistula results from its localization and symptomatic consequences. Fistulas can be internal or external. While fistulas between adjacent bowel loops are frequent and often not symptomatic, internal fistulas between distant sites (gastrocolic, rectovaginal, rec-

Key Words: Crohn’s disease; Fistula

Traitement des fistules chez les patients atteints de la maladie de Crohn: des antibiotiques aux anticorps

RÉSUMÉ : Les fistules sont fréquentes chez les patients atteints de la maladie de Crohn et, lorsqu’elles sont associées à un processus inflammatoire et qu’elles persistent durant plusieurs semaines, elles ont tendance à se chroniciser. Les fistules périnéales constituent la complication la plus fréquente et elles sont, la plupart du temps, associées à une atteinte du côlon. Leur traitement exige généralement la résection chirurgicale et une iléostomie permanente. Les antibiotiques, la cyclosporine, le méthotrexate et la thalidomide ont fait l’objet d’essais non comparatifs; seuls l’azathioprine, la 6-mercaptopurine et l’infliximab ont été évalués dans des essais menés à double insu, contre placebo. On a observé des rechutes avec tous les médicaments, sauf en cas de traitement prolongé. Chaque médicament est différent quant à son mode d’action et à sa tolérabilité à long terme. L’auteur propose une approche à l’égard du traitement des fistules dans le contexte de la maladie de Crohn.
tovesical) may cause severe complications (1). External fistulas are communications between the intestine and the skin; the most common sites of occurrence are the perineum and the abdominal wall. Because fistulas are usually associated with active inflammatory disease, they tend to be chronic. When fistulas are present for several weeks, spontaneous closure occurs uncommonly (2). In a placebo controlled trial (3), the rate of closure of chronic fistulas in patients not treated with an immunosuppressive drug was 6% over two years. Surgery itself has not changed the morbidity of fistulas much; improved parasurgical modalities, including parenteral nutrition, have been more beneficial in the general management of these patients (2,4).

The majority of lesions observed in therapeutic clinical trials of patients with fistulizing Crohn’s disease have been perianal and other enterocutaneous fistulas. Perianal fistulas are more often associated with colonic disease than with small bowel disease. One-third of patients with colonic Crohn’s disease have perianal fistulas; these patients are more likely to follow a chronic continuous disease course than patients without fistulas. The probability that a patient will require surgical resection (permanent ileostomy) due to fistula disease is increased in those with perianal fistulas (52% compared with 23% in those without perianal fistulas, at 20 years; relative risk 2.1) (5).

Various therapies for the management of Crohn’s disease have been reported to be effective in both uncontrolled and controlled trials. However, the effects of commonly used drugs such as 5-aminosalicylic acid, steroids and budesonide on fistulization have not specifically been reported. Also, recent clinical trials of novel therapies, such as Rh interleukin-10, Rh interleukin-11, intercellular adhesion molecule-1, antisense oligonucleotide and anti-integrin alpha-4, beta-7 monoclonal antibody, have not reported the outcomes of fistulas.

Most trials designed specifically to assess the closure of fistulas have been uncontrolled (antibiotics, cyclosporine, methotrexate and thalidomide); only two drugs – azathioprine (AZA) or 6-mercaptopurine (6-MP), and infliximab – have been evaluated in randomized, placebo controlled studies. Most of the trials have enrolled a small number of patients – usually patients who were refractory to other therapies and with enterocutaneous fistulas (perianal fistulas in the majority). End points have usually been defined (closure or improvement), although outcome criteria have not always been provided or have been variable among studies (improvement scale, time to response at onset or at a scheduled visit). Also, results have been reported differently, according to the number of fistulas or the number of patients with fistulas. Future studies should be standardized, for example by incorporating the perianal disease activity index (6) and the Present-Korelitz system (3).

ANTIBIOTICS

Metronidazole in a dose of 20 mg/kg, or 1000 to 1500 mg/day has been studied in three uncontrolled trials (7-9). Closure of fistulas occurred in 37%, 38% and 56% of patients, and improvement occurred in 63%, 62% and 28% of the 18, 26 and eight enrolled patients, respectively. Time to response varied from one to two weeks, to 9.1 weeks. After discontinuation of therapy, fistulas relapsed in 72% of 18 patients, but rapid healing was observed upon reintroduction of the drug (8).

In two studies, administration of ciprofloxacin alone (10) or with metronidazole (11) resulted in a closure rate of about 20% – lower than the rate achieved with metronidazole alone – and improvement occurred in 50% and 64% of the 10 and 14 enrolled patients, respectively.

AZA AND 6-MP

In a meta-analysis of five placebo controlled studies conducted between 1971 and 1980, closure or improvement of fistulas was observed in 54% of treated patients (22 of 41) and in 21% of patients taking placebo (six of 29) (odds ratio 4.44 [95% CI 1.50 to 13.20]) (12). A duration of treatment of more than 17 weeks was the strongest determinant of response of the active disease to the drug. Present et al (3), in a placebo controlled study, reported closure of 31% (nine of 29) versus 6% (one of 17) of fistulas and improvement of 29% (seven of 24) versus 18% (three of 17) of fistulas in patients treated with 6-MP versus placebo. Two subsequent uncontrolled studies in 1985 (13) and 1991 (14) reported closure rates of 37% and 23%, and improvement rates of 27% and 40% in 41 and 35 patients, respectively. The mean time to response with AZA 2.0 to 2.5 mg/kg or with 6-MP 1.5 mg/kg ranged from 3.1 to 4.5 months, with 20% of patients taking more than four months for improvement to be observed. Relapse occurred in all eight patients whose treatment was discontinued after closure of their fistulas (13). An uncontrolled study with an intravenous loading dose of AZA showed a closure rate of 54% (seven of 13), with a time to response of less than four weeks (15). However, a controlled trial of oral AZA with or without initial intravenous loading resulted in similar rates of complete response of active Crohn’s disease after eight, 12 and 16 weeks (16). Whether this observation also applies to closure or improvement of fistulas is unknown but is probable.

CYCLOSPORINE

Oral administration of cyclosporine has not been shown to be effective in the healing and maintenance of closure of fistulas (17). Better results have been obtained with an initial high dose of cyclosporine given intravenously (4 mg/kg) followed by an oral dose of 6 to 8 mg/kg. In three uncontrolled studies (18-20), closure or improvement of fistulas was observed in more than 80% of patients after only three to seven days. During oral maintenance therapy, healing of fistulas was maintained, but relapse was frequent after discontinuation of cyclosporine (five of seven patients) (20).

METHOTREXATE

In a retrospective review of 16 patients with fistulas, administration of methotrexate resulted in closure of 25% and
improvement of 31% (21). However, relapse was frequent after discontinuation of therapy.

INFLIXIMAB

Infliximab, a humanized chimeric monoclonal antibody to tumour necrosis factor-alpha, was recently assessed in a randomized, double-blind, placebo controlled study involving 94 patients with fistulas (22). After a median response time of two weeks, fistulas closed in 46% (29 of 63) and 13% (four of 31) of infliximab-treated and placebo-treated patients, respectively; improvement was also noted in 16% (10 of 63) and 13% (four of 31), respectively. Two doses of infliximab (5 and 10 mg/kg) were tested; the lower dose was associated with a higher response rate. There was a consistent treatment benefit regardless of concomitant therapy (eg, the presence or absence of therapy with AZA or 6-MP). However, the effect of treatment was not maintained; about 60% of patients with closed fistulas relapsed four months after the last infusion, and more than 90% relapsed 12 months after the last infusion (23). Overall, the median duration of response was three months (22). Infliximab was administered at zero, two and six weeks for the treatment of fistulas. A recent study showed that patients who failed to respond to the second infusion were unlikely to respond to the third infusion, suggesting that the last dose is not necessary to achieve the same results (24).

THALIDOMIDE

Two recent uncontrolled studies (25,26) involving patients with Crohn’s disease suggested that only a few weeks’ treatment with thalidomide may result in closure or improvement of fistulas; better outcomes were observed at doses between 100 and 300 mg/day.

ANECDOtal CASE REPORTS

Case reports have suggested a benefit of granulocyte colony-stimulating factor (27), oral tacrolimus (28) and clofazimine (29) in the treatment of fistulizing Crohn’s disease.

TOLERABILITY AND SAFETY OF DRUGS

In general, all drugs can be used safely by physicians who have experience with specific therapeutic modalities. Nevertheless, adverse events are common with all drugs and may lead to withdrawal of therapy.

Metronidazole, when used for several months at high doses, has been associated with side effects in almost all patients; these side effects often appear before the beneficial effects. The most common side effects are paresthesias due to peripheral neuropathy (about 50% of patients), metallic taste and gastrointestinal symptoms; all side effects are usually reversible after discontinuation of the drug (7,8). In one trial (8), six of 26 patients (23%) withdrew from therapy because of adverse events. Although the side effects were dose related, an attempt to reduce the dose of metronidazole resulted in the exacerbation of the fistulizing disease (8). While evidence of mutagenecity and carcinogenecity has been reported in animal studies, a risk has not yet been defined in humans.

Side effects resulting from high doses of cyclosporine include headache (50%), paresthesias (26%), hypertrichosis (13%), hypertension (11%), tremor (7%), renal insufficiency (6%), opportunistic infection (3%), gingival hyperplasia (2%), seizures (1%) and rarely anaphylaxis. The biggest issue that prevents the long term use of cyclosporine at high doses is the potential for permanent renal damage; infections and malignancy are other areas for concern (30).

In a trial using thalidomide 200 to 300 mg/day, sedation was reported to some extent by all patients, often requiring a reduction in the dose. Overall, three of the 22 patients (14%) discontinued the drug because of adverse events (25). The safety profile improved in a trial using a lower dose (50 to 100 mg/day); the most common side effects were sedation (58%), peripheral neuropathy (42%), edema (17%) and dermatitis (8%), and were reported to be mild and mostly transient (26).

For patients with inflammatory bowel disease (IBD), the overall rate of side effects with long term 6-MP treatment was 15%, including infections (7%), pancreatitis (3%), bone marrow depression (2%), allergic reactions (2%) and hepatitis (0.3%) (30). In a meta-analysis, withdrawal of therapy because of adverse events was reported in 27 out of 302 (8.9%) patients treated with AZA or 6-MP, and in six of 353 (1.7%) patients given placebo (12). The frequency of malignancy in patients treated over the long term with AZA or 6-MP for IBD has been reported to be 3% to 4% (31,32). Although this rate may represent an increased risk compared with that of control populations, it is suggested that the risk is due to an increased incidence of malignancy, mostly lymphoma, in patients with IBD (33).

In a trial using infliximab for the treatment of fistulas (22), side effects occurring more frequently with the active treatment than with the placebo were abscesses (11%), upper respiratory tract infections (10%) and fatigue (10%). One of the 63 (1.6%) patients treated with infliximab discontinued therapy because of pneumonitis. Concerns about infliximab relate to the development of antidual-stranded DNA antibodies, human antichimeric antibodies and the risk of autoimmune diseases, acute infusion reactions, delayed hypersensitivity reactions and lymphoma (34-37). Remission of the inflammatory disease can be maintained over one year by retreatment with repeated infusions every eight weeks for 36 weeks; there is general tolerability to this prolonged treatment, but one case of lymphoma and one case of suspected drug-induced lupus were reported in a study involving 73 patients (36). There is a potential for serum sickness reactions and delayed hypersensitivity reactions when treatment is repeated after long intervals (two to four years) between infliximab doses (34). These adverse events were not seen in other studies of infliximab involving 475 patients with rheumatoid arthritis receiving two or more subsequent infusions over eight to 38 weeks at fixed four- to 12-week intervals (35). A prelimi-
nary report on all patients prospectively observed up to three years after treatment in clinical trials suggested that the long term safety profile of infliximab is very good (38).

Toxicity reported to occur during low dose methotrexate treatment of autoimmune diseases such as psoriasis and rheumatoid arthritis includes diarrhea, mucositis, headache, central nervous system effects, hypersensitivity, pneumonitis, bone marrow suppression, hepatic fibrosis, or cirrhosis and lymphoma (30). In 94 patients with Crohn’s disease treated with methotrexate 25 mg administered weekly, 16 (17%) withdrew from treatment because of adverse events, including asymptomatic elevation of serum aminotransferase levels in seven (7%) and nausea in six (6%) (39). However, a lower dose of methotrexate (15 mg/week) in a selected group of patients who most previously entered into remission after treatment with 25 mg/week was associated with a good safety profile during 40 weeks of treatment (40). One of the major concerns about the long term use of low dose methotrexate in IBD patients is the potential for chronic liver disease. While a meta-analysis showed a 7% overall risk of developing severe fibrosis or cirrhosis in patients with psoriasis (41), the risk is much lower in patients with rheumatoid arthritis, at approximately 1% (42). The actual risk of developing histologically advanced liver disease is not known in patients with IBD.

DRUGS USED TO TREAT FISTULIZING CROHN’S DISEASE

Overall (Table 1), metronidazole and cyclosporine have a high efficacy in closing or improving fistulas, with an onset of action of a few days to a few weeks. However, neither drug provides sustained healing of fistulas, and both are rather poorly tolerated. Thalidomide shows promise in inducing closure or improvement of fistulas within weeks, but the sustained response is not known, and the drug has a rather limited tolerability for chronic use. AZA or 6-MP, and infliximab are effective in the treatment of patients with fistulas and are well tolerated under their current use; the time to response is short (two weeks) with infliximab and prolonged (three months or more) with AZA and 6-MP. Fistulas frequently relapse after discontinuation of therapy with all drugs; AZA and 6-MP are the only drugs with an established long term safety profile (30). The long term safety profile of infliximab requires additional clinical investigation.

Table 1: Drugs used for the treatment of fistulizing Crohn’s disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy (clos; global)</th>
<th>Onset of action</th>
<th>Relapse after D/C</th>
<th>Long term use and safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics (metro)</td>
<td>Very high (44%;&gt;90%)</td>
<td>Weeks</td>
<td>High</td>
<td>Poorly tolerated</td>
</tr>
<tr>
<td>Cyclosporine (high dose)</td>
<td>High (28%;&gt;90%)</td>
<td>Days</td>
<td>High</td>
<td>Poorly tolerated</td>
</tr>
<tr>
<td>Thalidomine (100 to 300 mg/day)</td>
<td>Mod high (46%;&gt;70%)</td>
<td>Weeks</td>
<td>Unknown</td>
<td>Limited tolerability</td>
</tr>
<tr>
<td>AZA/6-MP</td>
<td>Mod high (30%;60%)</td>
<td>Months</td>
<td>High</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Mod high (46%;60%)</td>
<td>Weeks</td>
<td>High</td>
<td>Probably well tolerated</td>
</tr>
<tr>
<td>MTX</td>
<td>Mod high (25%;55%)</td>
<td>–</td>
<td>High</td>
<td>Limited tolerability</td>
</tr>
</tbody>
</table>

AZA Azathioprine; Clos Closure; D/C Discontinuation; metro Metronidazole; Mod Moderately; 6-MP 6-Mercaptopurine; MTX Methotrexate

MANAGEMENT OF IBD FISTULAS

An ideal drug in the management of IBD fistula would treat the disease as well as the fistula; have a rapid onset of action; induce long term remission; be safe, easy to administer and monitor; and be cost effective. No single drug can achieve all of these goals. The best management strategy is to induce early closure because fistulas lasting more than four to eight weeks are likely to become chronic (2). Surgery has an important role in the initial treatment of external fistulas. Localized and conservative surgical interventions should be used to drain an abscess and/or to place Seton sutures (43). Because localized sepsis is often involved in its formation, initiation of drug therapy appears to be appropriate with the use of metronidazole. If closure does not occur within the early weeks, the objective is to avoid the development of complex and destructive fistulas. Once a fistula is chronic, there is debate as to the choice of treatment (Figure 1). The first step is to induce closure of the fistula with a fast-acting drug such as infliximab and maintenance with a long term drug such as AZA or 6-MP, or to start a remitting therapy with AZA or 6-MP followed, if needed, by the use of a drug such as infliximab that promotes closure. The last scenario is what clinical trials have designed so far. Infliximab is the drug of choice in these two scenarios because of its rapid onset of action and high clo-

Figure 1) Approach to fistulizing disease. AZA Azathioprine; 6 MP 6-Mercaptopurine
sure rate, and because its effect may last two months or longer after treatment. Repeated courses of infliximab have not been shown to be effective in keeping fistulas closed; the safety of repeated treatment over a one-year period has been shown in patients with active Crohn’s disease. Other fast-acting drugs do not usually maintain their effect long after discontinuation, and chronic or repeated administration of these drugs appears to be of limited long term tolerability. When a fistula fails to close, adjunctive therapy (antibiotics again, cyclosporine or tacrolimus, perhaps thalidomide) may be considered. At all times, if the active IBD persists, systemic corticosteroids should be avoided or used at the lowest dose. Indeed, steroid use has been associated with a poor prognosis for closure of enterovescical fistulas in one study (44), and this finding may also apply to other types of fistulas. Although surgery might be considered as the last intervention, this is unfortunately not a definitive cure in patients with IBD.

Because the course of Crohn’s disease is variable and largely unpredictable, an individualized approach to the treatment of fistulizing disease might be the preferred option based on the clinical situation, the patient’s preference and expectations of quality of life issues, the physician’s experience and local support for using a therapy and consequent cost-benefit compromise.

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