



## Treatment of Perianal Crohn's Disease

### Introduction

Perianal fistulas are a frequent manifestation of Crohn's disease and can result in significant morbidity, including scarring, fecal incontinence, and the need for surgery. Before 1970, therapeutic options were limited to antibiotics or surgery. During the past 30 years, the options for the medical treatment of fistulising Crohn's disease have changed dramatically. This article reviews these therapeutic options and their implications for disease management.

### Treatment Options

#### Azathioprine and 6-Mercaptopurine

Both 6-Mercaptopurine (6-MP) and its prodrug Azathioprine (AZA) are purine analogues that are frequently used to treat perianal fistulas. The details of fistula closure have been included in the results of 5 controlled trials of AZA/6-MP for Crohn's disease. A meta-analysis showed that 22 (54%) of 41 patients who received AZA/6-MP responded to treatment vs only 6 (21%) of 29 who received placebo. The pooled odds ratio was 4.44 in favour of fistula healing. The largest of these 5 controlled trials included 36 patients (40 fistulas, most of which were perianal) with fistulizing disease.<sup>[5]</sup> In this study, patients were treated with either 6-MP (1.5 mg/kg/day) or placebo for 1 year. Nine (31%) of 29 fistulas closed completely and 7 (24%) of 29 fistulas improved during treatment with 6-MP. In comparison, only 1 (6%) of 17 fistulas closed completely, and only 3 (18%) of 17 fistulas improved for patients on placebo. The incidence of adverse side effects in patients taking either 6-MP or AZA can range from 9.3%<sup>[6]</sup> to 15%.<sup>[8]</sup> The more common of these events include infections, pancreatitis, neoplasm, bone marrow suppression, allergy, and drug-induced hepatitis.

#### Anti-Tumor Necrosis Factor Alpha Antibody Therapy

Infliximab, an antibody targeted at TNF-alpha. A study of infliximab in 94 patients with fistulizing Crohn's received infusions at 0, 2, and 6 weeks of placebo, 5 mg/kg of infliximab. 62% percent of patients who received infliximab achieved the primary end point compared with 26% of the placebo cohort. Eleven percent of the patients treated developed an abscess, which was most likely secondary to the tendency for the cutaneous end of the fistula to close first, thus leaving an undrained pocket of sepsis. Efforts to establish effective drainage (incision and drainage of abscesses) and control of the rate of fistula closure to prevent uneven healing (ie, setons) should reduce the rate of abscess formation. The most common of these adverse effects included headache, nausea, and upper respiratory tract infections. Because of the murine component of the antibody, patients can develop antibodies after receiving infliximab.

#### Cyclosporine

Cyclosporine works by selectively blocking lymphocytes. This agent has also been used effectively for treatment of patients with fistulizing Crohn's disease. A total of 64 patients, have been published on the role of Cyclosporine in this disease setting. The overall initial response rate in these investigations was 83%. The clinical improvement with intravenous Cyclosporine given at a dose of 4 mg/kg/day is rapid and typically will occur within 2 weeks. Unfortunately, the response is not durable. Because of the high relapse rates and morbidity associated with cyclosporine, investigators have advocated it primarily as a "rescue therapy," using it as essentially a bridge to other safer, slower-acting medications, which may then be used as maintenance therapy.

#### Methotrexate

A number of studies have used Methotrexate successfully to treat Crohn's exacerbations, but its use in treating perianal disease has not yet been defined. To date, there has been only 1 small study published in abstract form using Methotrexate for fistulizing disease.<sup>[42]</sup> This study involved 16 patients with fistulas who were treated with 25 mg of Methotrexate intramuscularly each week. The precise duration of therapy and the time to response was not specified. 56% of the 16 patients taking methotrexate had a significant response, 25% of which had complete closure of their fistulas.

## **Thalidomide**

Thalidomide appears to be a potent inhibitor of TNF-alpha. Two small trials on the use of thalidomide in this clinical setting were recently published. Only a total of 32 patients with refractory Crohn's disease have been studied. Both studies showed good overall response rates at 12 weeks of ~60%. These initial pilot studies are certainly promising. However, the enthusiasm for thalidomide must be tempered by the risk of serious adverse effects, including teratogenicity, peripheral neuropathy, dermatitis, and excessive sedation.

## **Nutritional Therapy**

Elemental diets are composed of substances that are absorbed within the first meter of the small intestine.<sup>[46]</sup> This restriction limits the antigenic stimulation from the food and thus reduces the inflammatory process. Several studies have looked at the use of an elemental diet in treating Crohn's disease, which met with varying success.<sup>[47-52]</sup> In most of these series, the patients with perianal disease had a significantly lower response rate.<sup>[49-52]</sup> 6 patients with Crohn's perianal fistulas who were treated with an elemental diet and found that 4 improved. However, only 1 of 6 patients had complete healing of their fistulas. Except in rare instances, elemental diets are currently not used to treat perianal Crohn's disease.

## **Hyperbaric Oxygen**

Hyperbaric oxygen (HBOT) is used to increase the relative oxygen tension within the tissue. This increased oxygen environment is lethal to anaerobic bacteria. Increased oxygen tension can also improve leukocyte bactericidal activity and optimise fibroblast proliferation.<sup>[57]</sup> The initial articles on the application of HBOT in this disease setting were primarily individual case reports. 10 patients with refractory perianal Crohn's disease with HBOT. Eight of these 10 patients improved. However, 5 of the 8 patients who responded needed more than one course of therapy. The HBOT was administered in six 90-minute sessions each week, using 100% oxygen at 2.5 atmospheres of pressure. There were no associated complications. A 60% response rate using a similar HBOT protocol in 10 patients with refractory perianal Crohn's disease. In this study, 2 patients had to discontinue therapy because of adverse effects, which included bilateral tympanic perforation and psychological difficulties.

The considerable cost and time commitment associated with HBOT relegates its use to the small number of patients with severe refractory disease.

## **Conclusion**

Today, there are an increasing number of options for treating Crohn's perianal fistulas in the gastroenterologist's therapeutic armamentarium. The treatment of each patient's disease must, of course, be individualised. In general, antibiotics are used as the primary therapy for superficial or simple fistulas, either with or without surgical intervention. More complex fistulas require more intensive therapy. Combination therapy with antibiotics and AZA/6-MP with or without infliximab, along with conservative surgery (incision and drainage and seton placement), will facilitate the healing in most patients. For patients who do not respond to these intensive measures, tacrolimus provides a possible salvage therapy. Lastly, the growing number of alternative agents with unproven efficacy (ie, methotrexate, MMF, and thalidomide) have shown promising preliminary results. However, their use in widespread clinical practice must be reserved until their efficacy can be proven definitively.

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