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Mild to Moderate Crohn's Disease
An Evidence-Based Treatment Algorithm

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Contents

Abstract

Crohn's disease is a chronic inflammatory condition with a relapsing-remitting disease course. Treatment often requires both induction and maintenance strategies. The management of mild to moderate Crohn's disease is challenging because the natural history of mild disease is not known and effective treatment options are limited. In this article, our objective is to provide a brief overview of the evidence supporting current therapies in the treatment of mild to moderate luminal Crohn's disease and to explore a few of the newer therapeutic options.

As induction agents for mild to moderately active Crohn's disease, there is reasonable evidence to support the use of budesonide for terminal ileal and right colonic disease, and sulfasalazine for colonic disease. Although budesonide can be used in the short term (3–6 months) for maintenance of quiescent disease, there are no effective therapies for the long-term maintenance of mild to moderate Crohn's disease. Mesalazine appears to have no role in either the treatment of active or quiescent disease. Currently, there is insufficient data to draw conclusions on the potential role of antibacterials, probiotics or prebiotics.

Crohn's disease is a chronic inflammatory condition characterized by periods of inactivity and disease flare-ups; thus, treatment should involve both induction and maintenance strategies. Evidence-based therapeutic options for mild to moderate Crohn's disease are limited; in particular, effective maintenance agents for these patients are lacking. Although location and the severity of disease help guide therapy, the lack of correlation between endoscopic findings and symptoms pose a therapeutic challenge.[1]

In practice, severity is determined predominantly by symptoms and clinical factors such as haematocrit, extraintestinal manifestations and changes in bodyweight. As there are no standard indices, the severity of disease can often be difficult to quantitate. The Crohn's disease activity index (CDAI) is a tool used in randomized trials, but its utility is

limited and impractical in clinical practice. A CDAI score of 150–219 denotes mildly active disease and a score of 220–450 indicates moderately active disease.[2] The American College of Gastroenterology guidelines define mild to moderate Crohn's disease as ambulatory patients who can tolerate oral intake without evidence of dehydration, toxic features (fevers, rigors or prostration), abdominal tenderness, painful mass, obstruction or >10% weight loss.[3] Disease severity has also been classified on the basis of the type of medical or surgical intervention required and the response to these treatments. On the basis of this definition, mild disease reflects patients requiring only sulfasalazine, a 5-aminosalicylate, antimicrobials or topical therapy (including topical corticosteroids).[4]

In this article, we have elected to define mild to moderate Crohn's disease as patients not requiring the use of conventional corticosteroids, immunosuppressant therapy or biological therapy. Patients requiring more aggressive immunosuppressant therapy, such as systemic corticosteroids, are more aptly classified as moderate to severe because the natural history of disease in this group is likely to be different. We have also limited this discussion to the treatment of luminal Crohn's disease. Our aim is to briefly review the major studies supporting the use of the various agents in the treatment of mild to moderate luminal Crohn's disease and to propose a treatment algorithm (see figure 1).

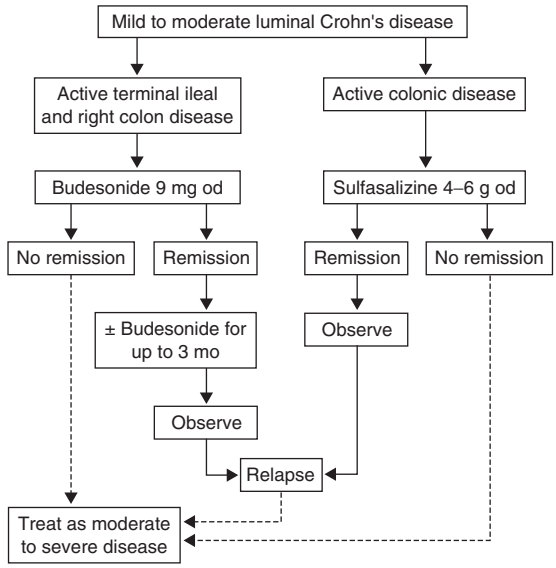

Fig. 1. Proposed treatment algorithm for mild to moderate Crohn's disease. **od** = once daily.

1. Natural History

The natural history of mild to moderate Crohn's disease is difficult to assess because most studies in this area are subject to referral centre bias. The majority of these studies are generated from tertiary or quaternary care centres, where patients tend to have more complex and severe disease than that seen in a community practice. Population-based studies may provide better insight into the natural history of mild to moderate disease.

Silverstein and colleagues[4] retrospectively examined a population-based inception cohort over a 24-year period to project the lifetime clinical course and long-term costs of care. In this analysis, a representative patient with Crohn's disease can expect to be in remission and not receiving medications for the majority of the clinical course (64%) of the disease and seldom require corticosteroid or immunosuppressive therapy (7%). Although most patients can be expected to remain 'well' for more than half of the projected lifetime, the periods of remission may not be contiguous or prolonged. A systematic review of the natural history of Crohn's disease in population-based patient cohorts from North America found that only 10% of patients have a prolonged remission. Most patients (73%) have a chronic intermittent disease course, while 13% have an unremitting disease course.[5] This review also found that in any given year, about 10% of patients are treated with corticosteroids. Bernstein and colleagues[6] examined the use of pharmaceuticals among inflammatory bowel disease patients in Manitoba, Canada, by reviewing the provincial prescription drug database for the year 1997. Among patients with Crohn's disease, 22.6% were prescribed oral prednisone, while 9.2% were prescribed an immunomodulator during that year.[6] These studies suggest that a large proportion of patients with Crohn's disease have a mild to moderate disease course based on our definition.

2. 5-Aminosalicylates

2.1 Sulfasalazine

Sulfasalazine is a prodrug that is metabolized by colonic bacteria via azoreductase into 5-aminosalicylic acid (5-ASA) and sulfapyridine. The active moiety in the treatment of inflammatory bowel disease was thought to be 5-ASA[7] and the sulfapyridine component was felt to be responsible for most of the adverse events of this medication, including headaches and gastrointestinal reactions. However, more recent data suggest that the sulfapyridine moiety may be a critical contributor to the mechanism of action of this drug. Sulfasalazine and not mesalazine was found to induce lamina propria T-lymphocyte apoptosis in patients with Crohn's disease.[8]

The efficacy of sulfasalazine in the treatment of active Crohn's disease was demonstrated in both the NCCDS (National Cooperative Crohn's Disease Study)[9] and the ECCDS (European Cooperative Crohn's Disease Study).[10] In the NCCDS, sulfasalazine 4–6 g/day for 17 weeks was statistically superior to placebo in the treatment of active Crohn's disease, resulting in a 43% clinical remission versus 30% in the placebo group. The benefit was most notable in colonic Crohn's disease. Similarly, in the ECCDS, sulfasalazine 3 g/day resulted in 50% clinical remission versus 38% in the placebo group. Sulfasalazine was not found to be effective in maintaining clinical remission in either of these studies. A smaller controlled trial consisting of 26 patients also found that sulfasalazine at 4–6 g/day for 26 weeks was effective in treating active Crohn's disease. However, in this study, the measure of response was based on an inflammatory index that is not widely used.[11]

2.2 Mesalazine

Mesalazine lacks the sulfapyridine moiety and thus is free of the sulfa-related adverse events. Although better tolerated, there is little evidence to support its efficacy in the induction or maintenance treatment of Crohn's disease.

In the study by Singleton et al.,[12] 310 patients with active Crohn's disease were randomized to Pentasa® [1] at 1, 2 or 4 g/day versus placebo for 16 weeks. A significant difference in remission rates was found between patients receiving Pentasa® 4 g/day (43%) versus placebo (18%) for both ileal and colonic Crohn's disease.[12] A subsequent meta-analysis of three 16-week randomized trials for active Crohn's disease (only the Singleton et al. study was published in its entirety) showed superiority of Pentasa® 4 g/day over placebo in reducing the CDAI score by 18 points. The clinical significance of this decrease is doubtful as most clinical trials define a response as a decrease in CDAI score of 70 or 100 points for a more robust outcome.[13]

Results from studies examining mesalazine as a maintenance agent are similarly unimpressive. Sutherland and colleagues[14] randomized 293 patients who achieved medical or surgical remission to mesalazine 750 mg four times daily versus placebo for 48 weeks. There was no significant difference in the relapse rates with 25% of patients in mesalazine group having relapse versus 36% in placebo group. Subgroup analysis showed significant differences in remission rates among women and those with ileocecal-colonic disease. Other studies using Asacol® or olsalazine (consisting of two 5-ASA molecules linked by an azo bond) reached similar conclusions with no difference in relapse rates between treatment groups versus placebo.[15,16] A Cochrane review of seven randomized controlled studies concluded that 5-ASA was not superior to placebo for maintenance of medically-induced remission in Crohn's disease.[17]

Overall, the balance of the evidence does not strongly support mesalazine use as an induction or maintenance agent in the treatment of Crohn's disease. In addition, if one considers the long-term costs of this treatment, it may outweigh any potential benefit. One study looking at the costs of care for Crohn's disease using Markov model analysis found that 5-aminosalicylate therapy accounted for 27% of the charges versus 13% for corticosteroids and immunosuppressive therapy, and 44% for surgery, which provided the longest remissions.[4]

Mesalazine is felt to be better tolerated than sulfasalazine as it lacks the sulfapyridine group; however, in terms of serious adverse reactions, it

1 The use of trade names is for product identification purposes only and does not imply endorsement.

may not be safer than sulfasalazine. One UK study looking at reported adverse events including interstitial nephritis, pancreatitis, serious skin reactions, hepatitis and blood dyscrasias concluded that there is no evidence to support a safety advantage of mesalazine over sulfasalazine.[18] Pancreatitis and interstitial nephritis were more common with mesalazine. Blood dyscrasias and hepatic disorders associated with sulfasalazine use were more frequently reported in patients treated for rheumatoid arthritis than inflammatory bowel disease. However, this study has been criticized for using spontaneous reports of adverse events because there is often under reporting.[19]

On the basis of the evidence to date addressing the benefits and risks of mesalazine for treating Crohn's disease, the use of this class of agents for treating Crohn's disease should not be supported.

2.3 Budesonide

Budesonide is a glucocorticoid with potent topical anti-inflammatory effects and low systemic bioavailability (~10%) as a result of high first-pass metabolism. It is associated with fewer adverse events than conventional corticosteroids. The controlled-release formulation is coated in ethylcellulose for time-dependent release targeted to the ileum and right colon. Studies comparing budesonide with placebo, mesalazine and conventional corticosteroids have shown efficacy for treatment of active Crohn's disease.

The studies of Greenberg et al.[20] and Tremaine et al.[21] were both placebo-controlled. The Greenberg et al.[20] trial comparing placebo versus budesonide 3, 9 and 15 mg/day showed the optimal dose administration for induction therapy to be 9 mg/day. The remission rates at 8 weeks were 20%, 33%, 51% and 43%, respectively, with the last two groups demonstrating statistically significant benefit over placebo. The Tremaine et al.[21] study did not show a statistically significant benefit over placebo, although the placebo rate was higher than expected. Thomsen et al.[22] compared budesonide 9 mg/day to mesalazine 2 g twice daily for 16 weeks and found statistically significant higher remission rates in the budesonide group over the mesalazine group at 8 weeks (69% vs 45%) and at 16 weeks (62% vs 36%).

There are a few studies comparing budesonide with conventional corticosteroids. The study by Rutgeerts et al.[23] compared budesonide 9 mg/day for 8 weeks, then 6 mg/day for 2 weeks with prednisolone 40 mg/day for 2 weeks, then tapering by 5 mg/day per week. The remission rate was 53% in the budesonide group and 66% in the prednisolone group at week 10.

A meta-analysis by Kane and colleagues[24] concluded that budesonide was more effective in inducing remission of active Crohn's disease than placebo and mesalazine. Budesonide was 13% less effective in inducing remission than conventional corticosteroids; however, in those with milder disease (CDAI score 200–300), there was no significant difference in remission rates. Budesonide was 35% less likely to cause corticosteroid-associated adverse effects than conventional corticosteroids.

The utility of budesonide as a maintenance agent was assessed by four randomized trials that utilized patients who entered remission in the induction trials.[20,25-27] The study design was common among these trials, with patients randomized to budesonide 6 mg/day, 3 mg/day or placebo for 12 months with the primary outcome being relapse, defined as CDAI score >150 and minimum increase of 60 points. In the Lofberg et al.[25] trial, the relapse rate at 3 months was significantly lower in the budesonide 6 mg group (19%) versus the 3 mg group (45%) and placebo group (44%); however, this benefit was lost by 12 months with relapse rates being 59%, 74% and 63%, respectively. Time to relapse was 258 days in the budesonide 6 mg group versus 139 days in the 3 mg group and 93 days in the placebo group. Similarly, Greenberg and colleagues[20] found a prolongation of time to relapse in the budesonide 6 mg group but there was no difference in relapse rates at 1 year. Hanauer and colleagues[27] found a trend towards prolonged time to relapse for budesonide 6 mg but again no difference in relapse rates at 1 year. In contrast, Ferguson and colleagues[26] found no significant difference at any timepoint in the relapse rates between the three treatment groups. As these trials had small sample sizes and are therefore subject to being underpowered, a predetermined pooled analysis of these four studies was performed by Sandborn and colleagues.[28] The authors concluded that budesonide

6 mg/day was effective for prolonging time to relapse, and for reducing rates of relapse at 3 and 6 months but not at 12 months. Therefore, there does not seem to be a role for budesonide in maintaining clinical remission.

2.4 Antibacterials

The possible aetiological link between pathogenic bacteria and the development of Crohn's disease have led to several studies exploring the therapeutic effects of antibacterials and probiotics. Despite this widely held belief that altering the gastrointestinal bacterial flora may have an impact on Crohn's disease, there is a paucity of data supporting the use of antibacterials in the treatment of active Crohn's disease.

Sutherland and colleagues[29] examined the utility of metronidazole in inducing remission and found no benefit. Patients were randomized to metronidazole 20 mg/kg, 10 mg/kg or placebo for 4 months. Although there was significant improvement in CDAI score, there was no difference in remission rates between the treatment and placebo groups. Only about half the patients enrolled completed this study. Subgroup analysis suggested metronidazole may be more effective in patients with disease confined to the colon. Another randomized trial examined the effect of antibacterials in addition to budesonide for the treatment of active Crohn's disease of the ileum and right colon.[30] All patients received budesonide 9 mg/day, but were randomized to receive either ciprofloxacin plus metronidazole both at 500 mg twice daily or placebo. Remission rate at 8 weeks was 33% in the antibacterial group versus 38% in the placebo group. In those with disease limited to the colon, there was a trend towards benefit for antibacterials. Remission was achieved in 53% among those treated with antibacterials versus 25% in the placebo group with a p-value of 0.10. Tolerance of antibacterials is an issue because the rates of discontinuation of medications as a result of intolerance was about 20%.

Prantera and colleagues[31] recently evaluated the use of rifaximin for the treatment of active Crohn's disease in a randomized, placebo-controlled trial. Patients with active mild to moderate Crohn's disease were randomized to rifaximin 800 mg once daily, 800 mg twice daily or placebo for 12 weeks. There was no significant difference among clinical remission rates (32%, 52% and 33%, respectively). However, remission and response rates were significantly higher in the twice-daily rifaximin group than the once-daily or placebo groups among the subgroup of patients with elevated C-reactive protein levels.

Although antibacterials may have a role in the treatment of active colonic Crohn's disease, further controlled studies targeting this subgroup are required.

2.5 Probiotics/Prebiotics

Most clinical trials investigating the use of probiotics for the treatment of active or quiescent Crohn's disease have been small, consisting of less than 50 patients. *Saccharomyces boulardii* and *Lactobacillus* GG have been studied as possible treatments for mild to moderate Crohn's disease.

S. boulardii was evaluated as maintenance therapy for Crohn's disease in a study with 32 patients with Crohn's disease in clinical remission.[32] Patients were randomized to mesalazine 1 g three times a day or mesalazine 1 g twice daily plus *S. boulardii* for 6 months. Clinical relapse was statistically significantly higher in the mesalazine alone group (37.5%) versus the mesalazine plus probiotic group (6.25%). Zocco[33] randomized 35 patients with quiescent Crohn's disease to *Lactobacillus* GG, mesalazine 2.4 g/day or *Lactobacillus* GG plus mesalazine 2.4 g/day. The relapse rates were similar in all three groups.

A Cochrane review published in 2006 concluded that there was no evidence to suggest a beneficial effect of probiotics in the maintenance of remission in Crohn's disease.[34] Some of the studies from this review were designed to assess maintenance in patients who have achieved surgical remission and are thus examining the role of probiotics in the prevention of post-operative recurrence.

A recent, small, open-labelled study examined the effect of a prebiotic in the treatment of active Crohn's disease. Ten patients with active ileocolonic Crohn's disease were given 15 g/day of fructo-oligosaccharides for 3 weeks. A significant reduction in Crohn's disease activity as measured by the Harvey Bradshaw index was demonstrated.[35]

Although small clinical studies have shown promise in treating patients with Crohn's disease by manipulating their bacterial flora through either pro- or prebiotic therapy, similarly to the state of antibacterial therapy for treating this disease, further studies are required before firm recommendations can be made.

3. Conclusion

Most patients with mild to moderate Crohn's disease will require induction and maintenance treatment because the majority of them will have a chronic relapsing disease course. Budesonide 9 mg/day has been shown to be superior to placebo as an induction agent for active terminal ileal or right colonic disease; however, as a maintenance agent it has only been shown to be effective at 6 mg/day for 3 months (supported by a randomized placebo-controlled trial) to 6 months (pooled analysis) and the efficacy of longer use cannot be recommended. Sulfasalazine at 3–6 g/day is an effective induction therapy for active colonic Crohn's disease but its use for maintenance of disease remission is uncertain. There appears to be no role for mesalazine in the treatment of active or quiescent mild to moderate Crohn's disease. The utility of antibacterials and probiotics is less clear. Studies evaluating antibacterials for active Crohn's disease have been negative, with subgroup analyses demonstrating possible benefit in patients with colonic disease. The limitations of long-term use of antibacterials are their tolerability and potential to negatively alter a patient's bacterial flora, creating antibacterial resistant bacteria and an environment more at risk for opportunistic infections such as fungal infections. Probiotics have not been proven to be useful for maintenance of Crohn's disease, but studies are small and therefore may be underpowered. Trials of prebiotics in the treatment of active Crohn's disease are emerging and they may prove to be a promising therapeutic option. Future larger studies evaluating bacterial manipulation are needed.

From an evidence-based perspective, certain medications such as budesonide and sulfasalazine have been shown to be effective to induce remission. What is a large deficiency in the field of Crohn's disease treatment is an effective and safe drug for maintenance of remission in patients with mild to moderate disease. We have proposed the treatment algorithm shown in figure 1 based on this current available evidence.

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