An Historical Overview of the Treatment of Crohn’s Disease: Why Do We Need Biological Therapies?

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Crohn’s disease is a disabling inflammatory bowel disease that may involve any part of the gastrointestinal tract. The disease decreases quality of life and leads to complications including stenoses, abscesses, and fistulae necessitating repeated surgeries and bowel resections. Until the late 1990s, standard therapies included mainly glucocorticosteroids, 5-aminosalicylic acid (5-ASA), antibiotics, and to a lesser extent, immunosuppression with azathioprine (AZA)/6-mercaptopurine (6-MP) or methotrexate. These therapies, especially glucocorticosteroids, mainly controlled symptoms without modifying the long-term disease course. Glucocorticosteroids also do not induce sustained mucosal healing. The lack of healing capacity mirrors the absent long-term efficacy of these drugs. Moreover, long-term use of glucocorticosteroids is associated with serious and sometimes irreversible side effects. AZA/6-MP are effective disease-modifying therapies that have been used in patients who are refractory to or relapse after steroids. Unfortunately, these agents have yet to have an established optimal benefit due to variations in genetically determined metabolism. With the advent of biologicals, new treatment aims have been advanced, including induction of remission with bowel healing both short term and long term, as well as reduction in the rate of complications, surgeries, and mortality. [Rev Gastroenterol Disord. 2004;4(suppl 3):S3-S9]

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Until the late 1990s, treatment of Crohn’s disease was primarily aimed at controlling symptoms of the disease. The drugs used until 1998 were mainly glucocorticosteroids, antibiotics, 5-aminosalicylic acid (5-ASA) and sulfasalazine, and immunosuppressives (Table 1). Maintenance of response
Historical Therapies in Crohn’s Disease continued

or remission was achieved only in a minority of patients, primarily utilizing immunosuppression with azathioprine (AZA) or 6-mercaptopurine (6-MP). These drugs were, however, used by few clinicians because of the lack of convincing clinical data and the fear of severe side effects. The frequent use of glucocorticosteroids resulted in the majority of patients suffering severe complications in the course of their disease because disease modification using drug therapies was not possible. Many patients underwent surgery at least once.

Furthermore, because Crohn’s disease is a chronic disabling bowel disorder occurring in mostly young adult patients during the most productive period of their lives, the quality of life was greatly decreased. The disease also causes a great psychological burden. Many patients encounter problems in their educational studies and professional life.

Drug Treatment of Crohn’s Disease

**Glucocorticosteroids**

Glucocorticosteroids induce remission in 48% of the patients with active Crohn’s disease and improve symptoms in another 32% within 30 days of initiating treatment, whereas 20% of the patients are resistant from the onset. At 1 year, however, 45% of the patients who experience initial improvement become glucocorticoid-dependent. Faubion and colleagues confirmed the limited efficacy of glucocorticosteroids for the treatment of Crohn’s disease and described similar results for ulcerative colitis. For Crohn’s disease, prolonged response at 1 year after the first course of glucocorticosteroids was achieved in only 32% of the patients, and for ulcerative colitis prolonged improvement was obtained in 49% of the patients. This suggests glucocorticosteroids are good induction agents but are not disease-modifying. Moreover, the long-term toxicity of systemic glucocorticosteroids is unacceptable. The major side effects are summarized in Table 2.

To avoid this toxicity, topically acting glucocorticosteroids have been developed, such as budesonide. This drug is somewhat less effective than prednisolone to induce remission but is associated with significantly fewer side effects and less suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Although topically acting glucocorticosteroids can be used for longer periods than systemic steroids, they also are not useful as maintenance agents. Relapse after weaning from glucocorticosteroids in responders with Crohn’s disease occurs early, and continued therapy with systemic glucocorticosteroids or topical formulations during 1 year after control of disease does not maintain remission. In summary, glucocorticosteroids were the mainstay of induction treatment until the late 1990s and are still used in many cases today though they lack efficacy for maintenance. The introduction of the topical drug budesonide allows more prolonged courses of therapy, but has not changed long-term outcomes.

**Aminosalicylates (5-ASA Drugs)**

5-ASA drugs are commonly used for the treatment of Crohn’s disease, but there is no placebo-controlled evidence for their efficacy. Sulfasalazine is only weakly effective in the treatment of active Crohn’s colitis and ileocolitis, whereas 5-ASA formulations are only slightly more effective than placebo to treat mild to moderately active Crohn’s disease. Sulfasalazine and 5-ASA formulations are also not effective for maintenance of remission after corticosteroids.

**Antibiotics**

Antibiotics are a potential alternative to glucocorticosteroids, although controlled evidence supporting their use is limited.
use is scarce. It is clear that enteric bacteria play a role in the pathogenesis of certain complications of Crohn’s disease, including abscesses and fistulae, and it is well established that bacterial overgrowth caused by strictures and blind loops responds well to antibiotic therapy. The fact that Crohn’s lesions are mainly located in segments of the bowel harboring extremely high bacterial counts and where the transit is slow suggests that bacteria play an important role. Also the initial role of the flora in the pathogenesis of colitis in animal models underscores the importance of the flora.

Metronidazole was first evaluated for therapy of Crohn’s disease by Ursing and Kamme. In a North American placebo-controlled trial of metronidazole, 105 patients with active disease were included, but only 56 completed the 16 week study. Two doses, 20 mg/kg and 10 mg/kg, of metronidazole were studied versus placebo. The Crohn’s Disease Activity Index (CDAI) decreased with 97 units, 67 units, and –1 unit, respectively (P = .002). The effect of the drug was most pronounced in patients with ileocolonic disease. Side effects of high-dose metronidazole therapy can be important and include mainly gastrointestinal intolerance, metallic taste, and neurotoxicity. Peripheral neuropathy can take months to reverse after discontinuation of the drug, and metronidazole is also teratogenic.

The quinolone antibiotic ciprofloxacin suppresses E. coli and aerobic enterobactericeae but has low activity against bacteroides and clostridium species. Ciprofloxacin achieves high fecal concentrations and is very effective against enteric pathogens, and also some species of mycobacteria. A study by Prantera and associates compared treatment with 1000 mg of ciprofloxacin and 1000 mg of metronidazole with methyl-prednisolone 0.70-1 mg/kg for 12 weeks. Forty-five percent (10 of 22) of the patients achieved remission with the antibiotics versus 63% (12 of 19) with methylprednisolone. The best results in the antibiotics group were observed after 6 weeks of therapy. Unfortunately, there are no studies on the long-term use of antibiotics to maintain remission in luminal disease.

**Immunosuppressants**

Immunosuppressants, also called antimetabolites, contrast with the aforementioned agents in that they are effective as maintenance agents. However, these drugs act slowly and hence are not useful for induction of remission. The success rate of immunosuppression with AZA or its metabolite 6-MP for maintenance is not completely clear. In a study by Candy and colleagues, 42% of patients treated with AZA were in remission at 15 months after induction with glucocorticosteroids as compared with only 7% treated with a placebo. Patients controlled with AZA for at least 6 months have an 11% chance of relapse at 1 year, 22% at 3 years, and 32% at 5 years. Young females with long delays in achieving remission are especially at risk of relapse. Approximately 15%
of patients do not tolerate AZA/6-MP, leaving only about half of patients who are responsive to AZA/6-MP in the treatment of steroid-refractory or steroid-dependent disease. Another 5% to 10% relapse, despite AZA/6-MP treatment. In addition, the efficacy of AZA or 6-MP seems much better in early Crohn’s disease in children than in adults. Markowitz and colleagues reported an 85% remission rate with 6-MP 1.5 mg/kg at 1 year after a 3-month induction with steroids versus 54% for placebo in children with steroid-dependent active Crohn’s disease. The toxicity profile of AZA/6-MP mainly includes myelosuppression, opportunistic infections, pancreatitis, and increased risk of lymphoma, although 10% to 15% of patients cannot tolerate these agents for nonspecific nausea or malaise.

Methotrexate, another immunosuppressant, at a dose of 25 mg intramuscularly (IM) per week induces remission at 12 weeks in 39% of patients with chronically active disease despite at least 3 months of steroid therapy and is an alternative for patients not responding to or intolerant of AZA/6-MP. Weekly methotrexate 15 mg IM maintained this remission in 65% of the patients in comparison with 39% with placebo. Methotrexate can induce myelosuppression and both hepatic and pulmonary fibrosis, and is also teratogenic.

**Fistulizing Crohn’s Disease**

A very disabling problem associated with Crohn’s disease is perianal fistulae. Fistulizing Crohn’s disease can involve the bowel but is more commonly present in the perianal region. Chronic perianal fistulae, which are secondary lesions to perianal or perirectal abscesses, significantly impair the quality of life in patients with Crohn’s disease, and acute perianal Crohn’s disease are a manifestation of disease activity frequently treated concomitantly with the bowel lesions. Spontaneous resolution occurs in up to 50% of patients. Control of sepsis is the first treatment aim, with the drainage of abscesses and placement of setons being an essential step. Severity and extent of the disease can be readily assessed by examination under anesthesia and by MRI. Endoscopic ultrasonography is sensitive but is hampered by the necessity for introduction of a large instrument in an often narrowed ano-rectum. Response to antibiotics is mostly incomplete and transient, although metronidazole and ciprofloxacin are useful frequently on a short-term basis to decrease or stop drainage, but relapse is immediate on discontinuation. Fewer than half of the patients with perianal fistulae respond to immunosuppression. For fistula healing, the mean time to response to 6-MP is 3.1 months with a maximal response at 8 months. A complete response is observed in 31% of the patients. Severe anal disease in non-responders often leads to stricture or incontinence due to destruction of the sphincter apparatus, which may necessitate proctectomy and colostomy or ileostomy.

**Healing of Gut Lesions**

Neither aminosalicylates nor antibiotics have been demonstrated to heal the bowel mucosa. Furthermore, the Groupe d’Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID) has demonstrated that high doses of prednisolone (1 mg/kg for 7 weeks) result in endoscopic remission in only 29% of the patients who had achieved clinical remission (92%), whereas no endoscopic remission was observed in 71% of the patients (93/131). Endoscopic lesions even worsened in 9% of patients treated with corticosteroids despite symptomatic improvement. This landmark study showed that glucocorticosteroids, although very efficacious in the short term to control symptoms, do not restore mucosal integrity in the ileum and the colon.

Contrary to the lack of mucosal healing with corticosteroids, data are available in the literature indicating that clinical improvement in patients treated with immunosuppressants can be associated with endoscopic healing. D’Haens and colleagues showed in an open trial that, in patients with severe post-surgical recurrence of steroid refractory ileal disease, treatment with AZA for at least 6 months resulted in healing of severe lesions. Six of 15 (40%) patients with durable clinical remission had healed their ileum completely with subtotal healing in 5 (33%) and partial healing in 3 (20%). There are no imaging data on the healing long term of perianal fistulae.
under the above mentioned historical therapies of Crohn’s disease.

**Discussion**

Until the late 1990s, medical therapy of Crohn’s disease was clearly deficient such that the majority of patients suffered from relapsing or chronic active disease and progressive disease resulted in a high proportion of complications. Before the era of biologicals and widespread use of immunosuppressive agents, only 42% of the patients with Crohn’s disease overall were relapse-free at 2 years after initial diagnosis and 12% after 10 years. Ten percent of the patients had continuously active disease at 2 years and 1% at 10 years.18

The cumulative probability of surgery for ileal or ileocolonic Crohn’s disease increased with the duration of disease and reached 60% at 10 years and more than 90% at 30 years.19 Crohn’s disease is indeed a disease of a lifetime. After ileocolonic resection 73% of the patients will have had endoscopic recurrence (new lesions in the neoterminal ileum) within 1 year after resection and 81% at 3 years.20 Clinical recurrence will occur in 20% to 30% at 1 year with an additional 10% per year thereafter. Between 30% and 50% of the patients will need a second resection within 10 years after the first surgical intervention.21 A small proportion of patients will end up having a short bowel with important nutritional consequences. In patients with colorectal Crohn’s disease,22 the cumulative risk of major surgery at 10 years after diagnosis amounts to 49%, and the risk for a permanent stoma approaches 25%. When Lapidus and coworkers22 compared the cumulative frequencies of surgery for the periods of diagnosis between 1960-1974 and 1975-1989, they found no significant differences; this clearly shows the lack of progress in medical treatment of Crohn’s disease. Only patients responding to immunosuppression did well for longer periods of time, emphasizing the lack of efficacy of these historical treatments (see Figure 1).

With the advent of biological therapies, new therapeutic goals have been defined. Treatments these days need to be “disease modifying.” They need to alter both short-term and long-term outcome of the disease. Short-term aims include the induction of complete clinical remission and healing of the bowel mucosa. Biological drugs alone or in combination with

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**Evidence-Based Use**

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Figure 1. Treatment of Crohn’s disease: From symptom control to disease control? 6-MP, 6-mercaptopurine; 5-ASA, 5-aminosalicylic acid; MTX, methotrexate.

New treatment methods must aim to be disease-modifying and must alter the disease, both short term and long term.
immunosuppressives should maintain clinical remission and mucosal integrity over the long term. This will lead to avoidance of complications including stenoses, abscesses, fistulae, and hence fewer hospitalizations, surgeries, and ICU stays, and less mortality. If the latter aims are achieved this will lead to an improved cost-utility ratio of treatments despite higher drug costs.

At present the indications for biological therapies in inflammatory bowel disease (IBD) can be summarized as follows. Definite indications are refractory luminal and perianal Crohn’s disease (including upper gastrointestinal disease), and steroid-dependent disease. Also, systemic manifestations including ankylosing spondylitis, pyoderma gangrenosum, chronic uveitis, and metastatic Crohn’s disease are important indications. Potential IBD indications for biological therapies include first line therapy (instead of glucocorticosteroids) for Crohn’s disease, ulcerative colitis, indeterminate colitis, refractory pouchitis, and primary sclerosing cholangitis. Since the introduction of infliximab in 1998, therapy of Crohn’s disease has greatly improved, but problems due to immunogenicity with loss of efficacy jeopardize the treatment in some patients. New biologicals, therefore, have been developed which will soon be introduced into clinical practice (Figure 1).

In summary, it is clear that before the introduction of biological therapy we could propose only treatments that offered mostly symptomatic relief to our patients. The current anti-cytokine therapies, especially anti-tumor necrosis factor agents, allow both control of symptoms as well as the potential to modify the course of disease.

References

Main Points
- Crohn’s disease is a disabling inflammatory bowel disease that can greatly decrease the quality of life and lead to stenoses, abscesses, and fistulae necessitating repeated surgeries and bowel resections.
- Until the late 1990s, standard therapies included glucocorticosteroids, 5-aminosalicylic acid, antibiotics, and immunosuppression with azathioprine/6-mercaptopurine or methotrexate.
- Glucocorticosteroids are good induction agents but are not disease-modifying and have long-term toxicity.
- Antibiotics are a potential alternative to glucocorticosteroids because evidence has shown that enteric bacteria play a major role in the pathogenesis of certain complications of Crohn’s disease. However, there are no studies on the long-term use of antibiotics to maintain remission.
- Immunosuppressants are effective maintenance agents, but they act very slowly, and hence are not useful for induction of remission.
- One of the most debilitating problems associated with Crohn’s disease is perianal fistulae.
- A major fault of standard therapies is that they do not heal the bowel mucosa in Crohn’s disease.
- With the introduction of new biological therapies, new therapeutic goals have been defined. Treatments need to be disease-modifying and need to treat the disease, both short term and long term.