Medical Management of Crohn Disease

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Abstract

Crohn disease (CD) is one of the major subtypes of inflammatory bowel disease and can occur in any segment of the alimentary tract. There have been significant advances in the medical therapy of CD over the past several decades. For mild CD, the oral corticosteroid derivative budesonide has demonstrated superior efficacy compared with traditional therapies such as 5-aminosalicylic acid, and can be used concurrently with these agents. For the management of moderate to severe disease, the immunomodulators azathioprine, 6-mercaptopurine, and methotrexate, as well as the antitumor necrosis factor- α (TNF- α) agents infliximab, adalimumab, and certolizumab pegol, have become the mainstay of therapy, with growing interest in combining these agents for maximal effect. Immunomodulators and anti-TNF- α agents have also demonstrated benefit in fistulizing CD. There has been growing evidence suggesting that both of these agents, along with the antibiotics metronidazole and ornidazole, are also effective in preventing postoperative recurrence of CD.

Keywords

- Crohn disease
- antitumor necrosis factor- α
- immunomodulators
- 5-aminosalicylic acid
- budesonide

Objectives: Upon completion of this article, the reader should be able to summarize the medications currently available for the management of mild, moderate to severe, and fistulizing Crohn disease, as well as those used for prevention of postoperative recurrence.

Crohn disease (CD) is one of the major subtypes of inflammatory bowel disease (IBD) and most commonly manifests with inflammation in the terminal ileum and cecum, though it can affect any segment of the alimentary tract. From a pathophysiological standpoint, CD is thought to represent an inappropriate response to the intestinal microbiome in genetically susceptible individuals. Given the autoimmune nature of CD, many of the therapies used for this disorder are targeted to reduce the inflammatory response. There are several pharmacologic options available to patients with CD, and therapy is often best tailored to the level of disease severity. With increased potency, there is an increased risk of deleterious side effects, such as increased rates of lymphoma and other malignancies, potentially life-threatening infections including fungal infections, lupus-like reactions, and bone marrow suppression.

This review will describe the currently available medication options for mild CD, moderate to severe CD, fistulizing

disease, and prevention of postoperative recurrence. With respect to mild CD, we will focus on local enteric therapies such as 5-aminosalicylic acid (ASA) and budesonide. For moderate to severe disease, we will discuss the thiopurines (azathioprine and 6-mercaptopurine), methotrexate, the newer monoclonal antibody-based agents, or “biologics,” such as infliximab, adalimumab, and certolizumab, and we will also address combination therapy with immunomodulators and biologics. With respect to fistulizing disease, we will discuss the role of antibiotics, immunomodulators, and biologic therapies, alone and in combination with seton placement. Lastly, we will explore the role of antibiotics, immunomodulators, and biologic therapy in the postoperative setting.

Mild Crohn Disease

Therapies for mild disease are aimed at alleviating symptoms while also minimizing medication-related side effects. The two main classes of medications most often utilized for mild disease are 5-aminosalicylate (5-ASA) and budesonide. Both of these agents are designed to work at the mucosal level, with reduced systemic absorption and effects.

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5-ASA was first synthesized in 1942.¹ Initially utilized to improve symptoms in patients with rheumatoid arthritis (RA), sulfasalazine (SASP) was incidentally noted to improve bowel-related symptoms in a subset of patients with colitis as well. However, doses above 2 to 4 g/day of this medication are often not tolerated by patients due to nausea and also may lead to more significant adverse effects, including fever, agranulocytosis, hepatitis, and methemoglobinemia. In 1973, Peppercorn et al demonstrated that the key active component of SASP and its derivatives was 5-ASA, which was released from cleavage of the azo-bond in SASP.² Since then, numerous preparations of 5-ASA-containing compounds have been developed, including pH-dependent and time-based release systems aimed at drug delivery to particular portions of the bowel, while eliminating the sulfa-based group that produced many of the more significant side effects.

The mechanism of 5-ASA in IBD remains poorly understood. There is growing evidence that this compound can affect several levels of the inflammatory cascade. 5-ASA has been shown to downregulate nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) levels, decrease levels of cytokines such as interleukin- (IL-) 1 and tumor necrosis factor (TNF), and inhibit T-cell proliferation, antigen presentation and antibody synthesis, and macrophage function.^{1,3-5}

There have been multiple randomized controlled trials (RCTs) assessing the efficacy of aminosalicylates in mild to moderate CD. A recent Cochrane analysis reviewed the results of these studies.⁶ Three trials assessed SASP versus placebo, with a total of 298 patients evaluated. These studies suggested improvement with SASP, with a relative risk (RR) of 1.51 (95% confidence interval [CI], 0.97–2.35). Eight studies examining mesalamine versus placebo for both response and induction of remission in mild to moderate CD did not demonstrate benefit over placebo when given at doses of 1 to 2 g/d. However, pooled analysis of three studies of delayed-release mesalamine at 4 g/day (Pentasa) versus placebo demonstrated a statistically significant decrease in mean Crohn's Disease Activity Index (CDAI) of 17.5 (95% CI, -35–0.1), the clinical impact of which is questionable. Both SASP and mesalamine, when compared with corticosteroids, did not demonstrate significant benefit.

Although the potential benefit of 5-ASA therapy is questionable and at best modest, its risks are minimal and therefore 5-ASA compounds remain part of the armamentarium for mild CD. Given the potential for inducing reversible renal insufficiency, it is suggested that patients on aminosalicylates have periodic monitoring of serum creatinine.

The other primary agent for mild CD is budesonide, a synthetic corticosteroid derivative taken orally. The majority of the medication's corticosteroid effect is delivered locally, and it is released in a time-dependent fashion in the terminal ileum and proximal colon. Upon absorption into the portal system, the drug is highly metabolized into significantly less-active metabolites in the liver (a concept known as "first-pass" metabolism), which reduces systemic exposure, potentially decreasing corticosteroid-related side effects, such as osteopenia and osteoporosis, fluid retention, elevated blood sugar,

insomnia, mood lability, acne, glaucoma and cataract formation, avascular necrosis, and adrenal insufficiency.⁷ Budesonide is taken orally, at doses up to 9 mg/day for up to 8 weeks, after which it is typically tapered over weeks or months before discontinuation.

There have been several trials evaluating the short- and long-term efficacy of budesonide in CD. In a double-blinded randomized controlled trial (RCT) published in 1994, 258 patients were randomized to receive daily budesonide at 3, 9, or 15 mg, or placebo. At 8 weeks, 51% of those receiving 9 mg and 43% of those receiving 15 mg budesonide were in remission, compared with 20% receiving placebo and 33% receiving 3 mg.⁸ Campieri et al compared budesonide 9 mg daily versus 4.5 mg twice daily versus prednisolone in 178 patients and found that 60% of patients receiving 9 mg budesonide or prednisolone were in remission at 8 weeks, compared with 42% in those receiving 4.5 mg twice daily.⁹ A systematic review by Seow et al evaluated the results of nine studies comparing budesonide to conventional corticosteroids, two studies comparing budesonide to placebo, and one comparing budesonide to aminosalicylates.¹⁰ Pooled analysis of the eight trials comparing budesonide to systemic steroids, with a total of 750 patients, found that budesonide was inferior to systemic steroids (RR, 0.85; 95% CI, 0.75–0.97). Three hundred twenty-seven patients were enrolled in the two trials evaluating budesonide versus placebo. At 8 weeks, the RR of remission was 1.96 (95% CI, 1.19–3.23) for those receiving budesonide 9 mg. A single RCT comparing budesonide to mesalamine was also included, with 182 patients, demonstrating a statistically significant improvement in rates of remission at 8 weeks (RR, 1.63; 95% CI, 1.23–2.16) and 16 weeks (RR, 1.79; 95% CI, 1.28–2.50). With respect to safety, six studies reported reductions in steroid-specific side effects in those taking budesonide when compared with systemic steroids, and three studies demonstrated no effect on cortisol levels with budesonide.

In summary, the main classes of medications used to treat mild CD are aminosalicylates and budesonide. Budesonide has been shown to have efficacy comparable to traditional corticosteroids, but with a reduced side-effect profile and efficacy superior to aminosalicylates. For these reasons, budesonide is considered first-line therapy for mild CD. Aminosalicylates have demonstrated, at best, modest efficacy at higher doses compared with placebo, and given their favorable side-effect profile, are still often utilized.

Moderate to Severe Crohn Disease

The initial therapy available for the acute management of CD has traditionally been systemic corticosteroids. Several early studies demonstrated the efficacy of corticosteroids in inducing remission in CD, with remission rates in up to 92% of patients.^{11,12} Despite the ability to induce remission, corticosteroids have not demonstrated equivalent efficacy at maintaining remission and are also known for significant long-term side effects.¹¹ Over the past 30 years, there has been significant research assessing agents that may allow for minimization of corticosteroid exposure. There are two

main classes of corticosteroid-sparing agents in moderate to severe CD: the immunomodulators, which include azathioprine (AZA), 6-mercaptopurine (6MP), and methotrexate (MTX); and the newer “biologics,” monoclonal antibodies against TNF- α , which include infliximab, adalimumab, and certolizumab pegol. In addition, there has been recent evidence suggesting that combination therapy with an immunomodulator and biologic may be the most efficacious and may potentially alter the underlying prognosis of CD.

Thiopurines

The thiopurines, which consist of AZA and 6MP, exert their effect via inhibition of purine synthesis. AZA is a prodrug, converted to 6MP within the host. Xanthine oxidase (XO) converts 6MP to the inactive metabolite 6-thiouracil. Allopurinol can be used to inhibit XO's function, shunting to conversion to the compound 6-TIMP. 6-TIMP is then either broken down by thiopurine methyltransferase (TPMT) to an inactive compound (6-MMPR) or converted to active 6-thioguanine nucleotide (6-TGN) (►Fig. 1). 6-TGN then functions as a purine analog, inhibiting DNA synthesis, and also appears to trigger T-cell apoptosis.^{13,14}

AZA and 6MP dosing must be carefully titrated due to potential marrow-suppressive and hepatotoxic effects. The goal dose of AZA is typically between 2 to 3 mg/kg/d, whereas the dose for 6MP is half this, at 1 to 1.5 mg/kg/d. As specific metabolites can lead to untoward side effects, it is advisable to measure TPMT genotype or enzymatic activity prior to initiation of therapy. A rare TPMT genetic variant, for which ~0.3% of individuals are homozygous, can result in decreased TPMT function and elevated levels of 6-TGN resulting in life-threatening marrow suppression.^{15,16} Approximately 11% of individuals are heterozygotes for this codominant mutation, requiring reduced dosing.

Two recent Cochrane analyses have synthesized the existing data regarding the efficacy of AZA and 6MP in the induction and maintenance of remission in CD.^{17,18} Prefontaine et al assessed eight RCTs of AZA/6MP for induction of remission in 425 patients with active CD.¹⁷ Overall response in the pooled treatment group was 54 versus 33% in the

placebo arm (odds ratio [OR], 2.43; 95% CI, 1.62–3.64). In addition to clinical response, five studies reported data on corticosteroid reduction while on these agents, with 76 of 117 (65%) thiopurine-treated patients exhibiting reduced steroid use, compared with 39 of 109 (39%) in the placebo group (OR, 3.69; 95% CI, 2.12–6.42). With respect to maintenance of remission, a recent systematic review assessing seven trials with AZA and one with 6MP demonstrated, among 550 patients, an OR of 2.32 (95% CI, 1.55–3.49) for AZA and 3.32 (95% CI, 1.40–7.87) for 6MP.¹⁸ A significant number of patients receiving AZA for maintenance of remission had to stop taking the medication due to intolerance, compared with placebo, with an OR of 3.74 (95% CI, 1.48–9.45).

Recent data has also demonstrated the utility for checking 6-TG levels in those who have not responded to therapy to optimize their dosing.¹⁹ Increasing AZA or 6MP dose dictated by metabolite levels results in improved outcome as opposed to when doses are modified discordant to these levels.²⁰

With respect to safety, thiopurine use requires careful laboratory monitoring, particularly when first initiating and titrating the drug. Pretreatment assessment of TPMT phenotype or genotype is recommended, and therapy should be avoided in those who are low metabolizers. Given the potential for significant bone marrow suppression, frequent CBC monitoring is recommended, particularly when initiating therapy or optimizing dosing. Liver function tests should also be monitored periodically. Thiopurines have also been associated with drug-induced pancreatitis. As with any form of chronic immunosuppression, there is an increased risk of infection. Lastly, the use of thiopurines has also been associated with a four- to sixfold increased risk of lymphoma and a two- to sixfold increase of nonmelanoma skin cancer.^{21–25} However, even though the relative risk of developing these cancers is increased, the absolute risk remains low.

Methotrexate

Methotrexate (MTX) is a folate analogue with potent anti-inflammatory properties. MTX inhibits dihydrofolate reductase, thereby inhibiting purine and pyrimidine synthesis, resulting in decreased cellular proliferation and modulation

Fig. 1 Metabolism of azathioprine and 6-mercaptopurine to their active and potentially toxic metabolites. AZA, azathioprine; DNA, deoxyribonucleic acid; 6-TU, 6-thiouracil; XO, xanthine oxidase; 6-MP, 6-mercaptopurine; 6-MMP, 6-methylmercaptopurine; 6-TIMP, 6-thioinosine 5'-monophosphate; TPMP, thiopurine methyltransferase; 6-MMPR, 6-methylmercaptopurine ribonucleotide; 6-TGN, 6-thioguanine nucleotide.

of cytokine production. MTX was first used in RA, and its efficacy was confirmed in several large RCTs in the 1980s.²⁶ The medication is administered intramuscularly (IM) or subcutaneously via weekly injections.

MTX was shown to induce remission in CD in a RCT by Feagen et al in which 141 patients with corticosteroid-dependent CD were randomized to receive weekly intramuscular MTX 25 mg or placebo.²⁷ Of the 94 patients receiving MTX, 37 (39%) were in remission at 16 weeks compared with 9 of 47 (19%) in the placebo arm (RR, 1.95; 95% CI, 1.09–3.48). Higher side-effect rates were present in the treatment arm, predominantly related to hepatotoxicity. Similar efficacy for induction of remission in active CD has not been appreciated at lower doses or in oral formulations, as demonstrated in a recent Cochrane review.²⁸ With respect to the use of MTX for the maintenance of remission in CD, a RCT by Feagen et al randomized patients to receive weekly intramuscular MTX 15 mg IM or placebo and found that of the 40 patients receiving MTX in this study, 26 (65%) remained in remission at 40 weeks, compared with 14 of 36 (39%) in the placebo group (OR, 0.36; 95% CI, 0.15–0.87).²⁹ Of the 36 patients who relapsed, 22 were given MTX 25 mg IM, 12 of whom (55%) were able to re-enter remission, compared with 14% of those not receiving MTX.

As with the thiopurines, there are significant potential side effects of MTX use. A common complication of MTX, given its mechanism of action, is folate deficiency. Therefore, patients taking MTX should also take folic acid, at a dose of 1 mg per day. Significant fatigue is common, as is nausea and alopecia. Though less common than with thiopurines, mild leukopenia can also occur. Hepatic fibrosis is a significant idiosyncratic effect of MTX, and liver function test monitoring is recommended, though transaminase levels may not correlate with degree of fibrosis. A recent meta-analysis demonstrated a rate of hepatotoxicity of 0.9 per 100 person-months and a rate of medication discontinuation for this side effect of 0.8 per 100 person-months.³⁰ Formal recommendations with respect to liver biopsy with cumulative dosages of MTX as seen in other diseases have not been made in IBD. Patients on long-term MTX should also be monitored carefully for new-onset cough or dyspnea, which could represent a rare, but potentially life-threatening drug-induced pneumonitis.

Anti-TNF- α Therapy

The monoclonal antibody-based medications infliximab (IFX), adalimumab (ADA), and certolizumab pegol (CZP), otherwise known as “biologics,” have become a mainstay of therapy for moderate to severe CD. TNF- α is a cytokine predominately produced by activated macrophages and lymphocytes, and has been shown to be elevated in the lamina propria of patients with CD. Agents such as IFX, ADA, and CZP function partly by binding soluble TNF- α and also by inducing apoptosis in activated T cells within the lamina propria of patients with CD. These agents have demonstrated the ability to induce apoptosis in activated monocytes, as well.^{31–33} IFX, administered intravenously, is a chimeric immunoglobulin G (IgG) antibody against TNF- α , containing both a human Fc segment and murine TNF- α binding region.³⁴ ADA, adminis-

tered subcutaneously, is a fully human antibody against TNF- α .³⁵ CZP, administered subcutaneously, is a pegylated humanized Fab' fragment of an anti-TNF- α antibody, without the Fc region.³⁶

Several studies have demonstrated the efficacy of IFX in inducing and maintaining remission in CD. Targan et al demonstrated the efficacy of a single dose of IFX at 5, 10, or 20 mg/kg versus placebo in a cohort of 108 patients with moderate to severe CD with 4-week response rates of 81, 50, and 64% for patients receiving IFX at 5, 10, and 20 mg/kg, respectively, compared with 17% for the placebo group ($p > 0.001$).³⁷ In the ACCENT I trial, 573 patients were initially given IFX 5 mg/kg, and the 335 patients (58%) who responded within 2 weeks were randomized to receive continued infusions of IFX at 5 or 10 mg/kg versus placebo at weeks 2, 6, and then every 8 weeks.³⁸ At 30 weeks, patients receiving IFX at 5 and 10 mg/kg had significantly higher rates of remission compared with placebo (39 and 45%, respectively, vs. 21%; combined OR, 2.7; 95% CI, 1.6–4.6). This difference remained statistically significant at 54 weeks. Patients receiving IFX also had higher rates of corticosteroid cessation (OR, 4.2; 95% CI, 1.5–11.5).

Similar efficacy in inducing and maintaining remission has been demonstrated with ADA. The CLASSIC-1 trial assessed the efficacy of two doses at weeks 0 and 2 of ADA at three dosing levels (40/20, 80/40, and 160/80 mg) compared with placebo in anti-TNF- α naïve patients with active CD. The highest dose of 160/80 mg demonstrated significantly higher rates of remission at week 4 (36 vs. 12%, $p = 0.001$).³⁹ In the CLASSIC II trial, 55 patients who remained in remission after receiving two doses of ADA within CLASSIC I at 4 weeks were randomized to receive either ADA 40 mg every other week (EOW) or weekly, or placebo.⁴⁰ Those not still in remission at 4 weeks after CLASSIC I were eligible for inclusion in an open-label treatment arm within CLASSIC II. Patients in the randomized arms of the trial were permitted to enter the open-label trial if they flared, as well. At 56 weeks, 79 and 83% of patients receiving ADA EOW and weekly, respectively, were in remission, compared with 44% in the placebo arm ($p < 0.05$ for each group compared with placebo). In the open-label arm, 46% of patients receiving ADA were in remission at 56 weeks.

The CHARM study assessed the efficacy of ADA in the maintenance of remission in patients who had and had not received IFX.⁴¹ Similar to CLASSIC-II, 778 patients received two doses of open-label ADA, after which all patients were randomized in a stratified fashion based on response and prior IFX to receive ADA 40 mg every other week (EOW) or weekly, or placebo. Remission rates were higher in both ADA groups at week 26, with 40% of weekly recipients and 47% of EOW recipients in remission, compared with 17% receiving placebo ($p < 0.001$ for both ADA groups compared with placebo). A significant number of patients remained in remission at week 56, with 36 and 41% for ADA weekly and EOW, respectively, compared with 12% for placebo ($p < 0.001$ for both ADA groups compared with placebo). Of note, IFX naïve patients had numerically higher response rates than those with prior IFX exposure.

Similar results were demonstrated for induction and maintenance of remission with CZP in the PRECISE-1 trial.³⁶ The WELCOME trial demonstrated efficacy of CZP in patients who had previously lost response to IFX.⁴²

The increased potency and efficacy appreciated with the biologic agents also comes with an increased risk of adverse events. As with the immunomodulators, significant immunosuppression with biologics is thought to increase the risk of opportunistic and fungal infections and malignancies such as lymphoma and nonmelanoma skin cancers.^{21–25} Whether this risk can be attributed to anti-TNF agents or concomitant use of other immunomodulators remains controversial, however. Recent analysis of pooled data from several clinical trials suggests that these risks may not be as elevated with anti-TNF agents when used alone, but appear to be increased when receiving both anti-TNF drugs and immunomodulators.⁴³ In addition, anti-TNF therapy has been associated with drug-induced lupus, demyelinating reactions, peripheral neuropathy, psoriasis, and heart failure.

Combination Therapy

There has been growing interest in the use of early combined therapy with immunomodulators and biologics in moderate to severe CD. As opposed to traditional “step-up” therapy, such “top-down” therapy has been hypothesized to potentially reduce long-term corticosteroid exposure and modify the overall disease course in IBD. The addition of an immunomodulator to a biologic may not only act synergistically in treating the underlying disease, but also functions to inhibit the formation of antibodies against the biologic, thereby increasing trough levels.

The efficacy of combination therapy was recently assessed in a large, multicenter RCT, SONIC, in which 508 patients were randomized to receive AZA + placebo, IFX + placebo, or AZA + IFX for 30 weeks, with the option to continue in a blinded fashion to 50 weeks.⁴⁴ Corticosteroid-free remission at week 26 was achieved in 57% of patients receiving combination therapy, compared with 44% receiving IFX monotherapy ($p = 0.02$) and 30% receiving AZA monotherapy ($p < 0.001$). Those who underwent endoscopy at week 26 demonstrated higher rates of mucosal healing compared with infliximab and AZA as well. Patients receiving combination therapy had lower rates of antibody formation to IFX as well as higher IFX trough levels compared with their IFX monotherapy counterparts. Rates of serious infection were not significantly different between groups. However, the long-term sequelae of combination therapy are still inadequately described; it is possible that combination therapy does increase the risk of serious infection and malignancy.⁴³

In summary, several corticosteroid-sparing agents have been assessed over the past 30 years. AZA/6MP and MTX have demonstrated efficacy in inducing and maintaining remission, but require monitoring for bone marrow suppression and hepatotoxicity. The newer biologic agents have demonstrated superiority to placebo, and in SONIC to AZA as well. They appear to have even high efficacy rates when combined with an immunomodulator, but this may increase the risk of infection and malignancy long term.

Fistulizing Crohn Disease

Fistula formation is a common complication in CD. These lesions often require surgical therapy and seton placement, particularly when cutaneous involvement is present. When considering therapy for fistulas, it is important to assess whether these fistulas are simple or complex. Simple fistulas are superficial, have only one opening, are not rectovaginal, and are not associated with stricture or abscess. Complex fistulas are supra- or intrasphincteric, have more than one opening, and are associated with abscess or stricture. Antibiotics have been a mainstay of therapy for simple fistulizing disease, while those with complex features are typically treated with a combination of approaches including immunomodulators, biologics, and seton placement.

Antibiotics such as ciprofloxacin and metronidazole historically were considered to be first-line treatment for the management of fistulizing disease, despite limited data evaluating their efficacy. A recent study attempted to address this paucity of data, but was itself limited by poor recruitment.⁴⁵ Twenty-five patients with CD and draining perianal fistula were randomized to receive ciprofloxacin 500 mg, metronidazole 500 mg twice daily, or placebo for 10 weeks. Fistula closure at 10 weeks was observed in 30, 0, and 13% of patients receiving ciprofloxacin, metronidazole, and placebo, respectively, whereas fistula improvement was seen in 40, 14, and 13% of patients receiving ciprofloxacin, metronidazole, and placebo, respectively. Thus, larger trials are required to further assess the role of antibiotics in fistulizing disease.

Thiopurines have demonstrated efficacy in fistula closure in CD in a RCT of 36 patients with 44 fistulas who were treated with 6MP or placebo.⁴⁶ Fistula closure was observed in 31% of patients receiving 6MP versus 6% in placebo, with fistula improvement seen in 55 versus 24%.

Biologics have also demonstrated efficacy in fistula healing. IFX first demonstrated efficacy in fistulizing CD in a study by Present et al, in which patients with draining abdominal or perianal fistulas of > 3 months duration were randomized to receive IFX at 5 or 10 mg/kg, or placebo.⁴⁷ Fistula improvement was seen in 68 and 56% of patients receiving IFX at 5 and 10 mg/kg, respectively, compared with 26% of those receiving placebo ($p = 0.002$ and $p = 0.02$ compared with placebo, respectively). Both doses also had significantly higher rates of complete fistula closure compared with placebo as well. The ACCENT II trial also assessed the efficacy of maintenance IFX therapy in patients with CD complicated by single- or multiple-draining perianal, enterocutaneous, or rectovaginal fistula.⁴⁸ In this RCT, 195 of 282 patients with an initial response to three doses of IFX 5mg/kg were randomized at 14 weeks to continued IFX 5 mg/kg every 8 weeks or placebo. At 54 weeks, 23% of those randomized to placebo still had reduced fistula output, compared with 46% receiving maintenance IFX ($p = 0.001$), with 36% of IFX patients maintaining a complete response, compared with 19% in the placebo arm ($p = 0.009$). In addition, the ACCENT II trial demonstrated significant efficacy of IFX in a subset of 25 patients with complex rectovaginal fistulas.⁴⁹ Closure rates remained persistently higher in the IFX arm (55–90%) compared with

placebo (29–43%) during the 1-year follow-up period. Median duration of response was longer in the maintenance arm as well (46 vs. 33 weeks). Similarly, ADA demonstrated efficacy for the treatment of fistulizing CD in the CHARM trial, with 30% of patients demonstrating complete fistula closure at week 26 compared with 13% of placebo ($p = 0.04$); this response was durable at 56 weeks.⁴¹ With respect to CZP, the PRECISE-2 trial reported that 36% of patients receiving CZP had complete closure of their fistula at 26 weeks, compared with 17% of those receiving placebo ($p = 0.04$).⁵⁰

Several small studies have examined combination therapy in fistulizing CD. One case series of 16 patients receiving a thiopurine and IFX demonstrated that 75% of patients had fistula closure.⁵¹ Another study of 12 patients receiving MTX and IFX noted 33% sustained fistula closure for > 6 months, with three others noting partial improvement.⁵² Although encouraging, larger studies of combination therapy are still required.

The most promising option for fistula therapy may be the combination of seton placement and a biologic. A retrospective study of nine patients receiving IFX and seton placement demonstrated 100% response rate, compared with 83% in those receiving IFX alone; patients receiving seton placement with IFX also had lower recurrence rates compared with IFX alone and longer time to recurrence.⁵³ A subsequent randomized trial of 35 patients receiving IFX and seton versus either therapy alone found that patients receiving both IFX and seton had a significantly longer time to relapse.⁵⁴

In summary, biologic therapy, particularly when combined with seton placement, may represent the best approach for more complex fistulizing disease. Immunomodulators remain an option for both complex and simple fistulas as well. Antibiotics have minimal evidence supporting their use, but are still used for simple fistulas.

Postoperative Recurrence

Epidemiologic studies have demonstrated that up to 32% of patients with CD will require surgery within the first 10 years of disease.⁵⁵ Antibiotics, thiopurines, and IFX have been assessed to potentially prevent postoperative recurrence. Two trials have assessed the efficacy of nitroimidazoles for the prevention of postoperative CD recurrence after ileal resection. Metronidazole was assessed in a study of 60 patients randomized to the antibiotic or placebo starting 1 week postoperatively and continued for 3 months.⁵⁶ Recurrence of clinical symptoms was reduced in those receiving metronidazole, with 4% of patients having clinical recurrence at 1 year, compared with 25% of those receiving placebo ($p = 0.044$). There was also a nonsignificant reduction in the endoscopic rate of recurrence at 12 weeks. Rutgeerts et al also assessed the efficacy of one year of therapy with ornidazole in 80 patients and found that clinical and endoscopic recurrence rates at 1 year were significantly reduced with this antibiotic (8 and 54%, respectively) compared with placebo (38 and 79%, respectively).⁵⁷ However, 32% of patients receiving ornidazole had to discontinue the study

medication due to side effects, compared with 13% of those receiving placebo ($p = 0.041$).

Thiopurines have also demonstrated benefit in the prevention of postoperative recurrence. Hanauer et al assessed the efficacy of 6MP compared with 5-ASA and placebo in 131 patients with CD over 24 months.⁵⁸ In this RCT, 50% of patients receiving 6MP were in clinical remission at 24 months, compared with 42% of those receiving 5-ASA (hazard ratio [HR], 0.62; $p = 0.123$) and 23% receiving placebo (HR, 0.52; $p = 0.045$). Similarly, 6-MP demonstrated reduced rates of endoscopic recurrence (43%) compared with 5-ASA (63%) and placebo (64%), though this was only statistically significant with the placebo comparator.

The efficacy of combined metronidazole and AZA versus AZA alone was assessed in a study of 81 patients with CD who were at high risk of disease recurrence.⁵⁹ At 12 weeks, 34% of patients receiving both metronidazole and AZA had endoscopic recurrence, compared with 53% of those receiving metronidazole alone ($p = 0.11$). Rates of endoscopic recurrence were lower at 12 months as well, with 44% receiving metronidazole + AZA demonstrating evidence of recurrence compared with 69% receiving metronidazole alone ($p = 0.048$).

IFX has also demonstrated potential benefit in preventing postoperative recurrence in a recent study of 24 patients randomized to receive IFX or placebo starting 4 weeks postoperatively for 1 year.⁶⁰ In this study, 1 of 11 patients (9%) receiving IFX had evidence of endoscopic recurrence, compared with 11 of 13 (85%) in the placebo group ($p = 0.0006$). Clinical remission was maintained in 80% of the treatment group, compared with 54% in the placebo group ($p =$ nonsignificant). Larger trials are needed to further assess this potentially beneficial option for preventing postoperative recurrence.

Conclusion

The past three decades have borne a marked expansion in available medical therapies for CD, from application of older medications such as the thiopurines and MTX, to the development of new corticosteroid formulations designed to lower systemic side effects and monoclonal antibodies against specific cytokines. These advances have led to a paradigm shift in how we view the treatment of moderate to severe disease. For mild disease, budesonide has demonstrated superiority to aminosalicylates, which can also be used adjunctively. For moderate to severe disease, combination therapy and biologic therapy have demonstrated superiority to the immunomodulators, although particularly with combination therapy, the long-term side effects of such potent immunosuppression require further study.

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