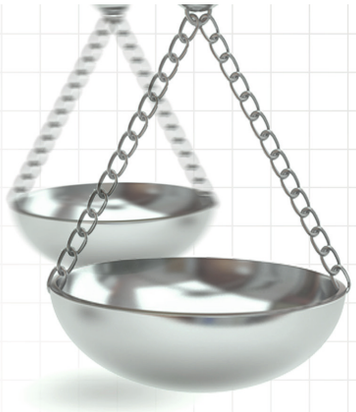

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REVIEW

# Comparing medical treatments for Crohn's disease

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**The drugs available for inflammatory bowel disease are aminosalicylates, antibiotics, steroids, immunosuppressors and biologics. The effectiveness of these drugs has been evaluated in many randomized clinical trials, mainly versus placebo. Few studies have been conducted comparing the different drugs among themselves, owing to the methodological problems raised by comparative trials, such as sample size and blindness. This review focuses mainly on the randomized clinical trials that have compared different treatments. Of course comparisons are mainly between drugs used in a particular setting (mild, moderate and severe disease). However, on many occasions there is no homogeneity in these clinical settings, and therefore the results are difficult to interpret.**

Crohn's disease (CD) is a chronic disorder, characterized by transmural inflammation of the bowel. Phases of remission and relapse occur during the course of CD [1,2] and over time complications such as strictures, fistulas or abscesses could be present [3]. More than 50% of fistulas involve the perianal region and this kind of complication may be a significant cause of morbidity [4]. Furthermore, surgical resection, due to a complication or therapeutic failure, is a predictable event through the course of CD and the surgical rate increases with time [5]. However, surgery is not curative and 1 year after resection more than 50% of patients show an endoscopic recurrence and approximately 20% will develop a clinical relapse [6].

Clinical expression of CD is heterogeneous with a wide spectrum of patterns and different clinical courses, so it is not easy to find the best therapy for all patients. The therapeutic benefit of old and new drugs has been investigated and is still investigated in the different settings of CD. This review aims to compare the efficacy of the available therapies in every relevant setting: active CD, quiescent CD (maintaining remission), postsurgical CD (prevention of relapse after surgical resection) and fistulizing CD. The review, when possible, focuses on the comparison between drugs. However, the comparison between different drugs is often difficult because of the heterogeneity of the disease and much of the evidence comes from comparison with placebo.

## Active CD

Most studies have evaluated these drugs versus placebo, few have compared different drugs (Table 1). According to the European Crohn's and Colitis Organisation (ECCO) guidelines, the treatments of choice for mild-to-moderate active CD are aminosalicylates (in colonic CD), budesonide or systemic corticosteroids [7]. In moderate-to-severe active CD, conventional corticosteroids must be considered to be the treatment of choice for induction of remission. Immunosuppressants may be used in the case of intolerance, dependency or refractoriness to steroids, but their role in active CD is not relevant due to their slow onset of action [8]. The use of anti-TNF-α agents must be considered in patients who do not respond to conventional therapies.

### ■ Aminosalicylates

The benefit of aminosalicylates for the treatment of active CD is considered to be limited [7]. The first aminosalicylate used for the treatment of CD was sulfasalazine



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**Table 1. Trials comparing treatments in active Crohn's disease.**

| Study (year) | Compared treatments | Most effective treatment | Ref. |
|---|---|---|---|
| Summers *et al.* (NCCDS) (1979) | Prednisone/SASP/AZA | Prednisone | [9] |
| Malchow *et al.* (ECCDS) (1984) | 6-methylprednisolone/ SASP | 6-methylprednisolone | [10] |
| Thomsen *et al.* (1998) | Budesonide/5-ASA | Budesonide | [14] |
| Tromm *et al.* (2011) | Budesonide/5-ASA | No significant difference | [15] |
| Oren *et al.* (1997) | MTX/6-MP | MTX | [37] |
| Neurath *et al.* (1999) | Mycophenolate/AZA | Mycophenolate | [38] |
| Reinisch *et al.* (2008) | Everolimus/AZA | AZA | [39] |
| Colombel *et al.* (SONIC) (2010) | Infliximab/AZA/ Infliximab + AZA | Infliximab + AZA | [40] |
| Lemann *et al.* (2006) | Infliximab + AZA/AZA | Infliximab + AZA | [41] |
| Ardizzone *et al.* (2003) | MTX/AZA | No significant difference | [46] |

AZA: Azathioprine; MTX: Methotrexate; SASP: Sulfasalazine.

(SASP). Two old studies compared SASP with placebo in active CD, showing that SASP was only marginally superior to placebo in mildly active CD but a modest efficacy was reported in patients with colonic CD than in patients with ileal CD [9,10]. In a meta-analysis, the efficacy of 5-aminosalicylic acid (5-ASA), the active component of SASP, was compared with placebo [11]. At week 16, 5-ASA was found to be superior to placebo in mild active CD, with a significant improvement in the Crohn's Disease Activity Index (CDAI) value. Despite this positive result, the meaning of the reduction in CDAI value as a clinical outcome of efficacy is debatable. Furthermore, in this meta-analysis the negative result of a trial by Singleton *et al.* was not included, making the conclusions unreliable [12]. In a more recent meta-analysis, nine trials evaluating the efficacy of 5-ASA in active CD were reviewed [13]. No significant difference was observed between 5-ASA and placebo or conventional steroids in terms of clinical remission. A trend towards a benefit of SASP with respect to placebo was observed.

Two studies compared the efficacy of 5-ASA with that of budesonide. In the first study published more than 10 years ago, clinical remission was observed more frequently with budesonide than with 5-ASA [14]. In the more recent study, budesonide was not found to be statistically more effective than 5-ASA in mild-to-moderate CD [15]. The result of this last study is questionable because the efficacy of 5-ASA was found to be higher compared with other studies and this is difficult to explain.

### Corticosteroids

Conventional corticosteroids, prednisone and 6-methyl prednisolone, have traditionally been the most commonly used drugs for induction of remission in CD. In the first two trials evaluating the efficacy of corticosteroids in active CD, a significantly higher rate of patients treated with corticosteroids achieved remission at week 17 compared with patients treated with placebo, SASP or azathioprine (AZA) [9,10]. In a Cochrane meta-analysis, eight studies comparing corticosteroids with placebo (two studies) or with 5-ASA (six studies) were reviewed [16]. Corticosteroids were found to be more effective than placebo and 5-ASA at inducing remission in CD. A more recent review confirmed the efficacy of corticosteroids compared with placebo and 5-ASA in active CD [17].

Although the efficacy of corticosteroids in active CD is clear, approximately 20% of patients do not respond to this therapy and should be treated with other drugs [18].

### Budesonide

Budesonide is a controlled ileal release formulation of corticosteroid, characterized by a topical activity with limited systemic action, due to its rapid hepatic metabolism [19]. The use of budesonide is indicated in mildly and moderately active ileo–caecal CD, before conventional corticosteroids [7].

Two trials have been conducted comparing budesonide with placebo in the treatment of active CD [20,21]. In the first trial, patients were treated with three different doses of budesonide (3, 9 and 15 mg daily) or placebo [20]. At week 8 clinical remission was achieved in a higher rate of patients treated with budesonide 9 mg daily compared with patients treated with placebo. The incidence of adverse events did not differ between the budesonide groups and the placebo group. In the second trial, patients were treated with budesonide 9 mg daily, 4.5 mg twice daily or placebo [21]. At week 8 no differences in terms of clinical remission were observed between the three groups of patients.

In a Cochrane meta-analysis twelve studies, comparing budesonide with conventional corticosteroids, 5-ASA or placebo, were reviewed [22]. After 8 weeks of treatment, budesonide was found to be more effective than placebo

and 5-ASA, but less effective than conventional corticosteroids for induction of remission, mainly in patients with severe disease. A more recent meta-analysis confirmed the superiority of budesonide compared with placebo but not compared with conventional corticosteroids [17]. With regard to the side effects, all of the meta-analyses reported a lower incidence of steroid-related side effects in patients treated with budesonide compared with patients treated with conventional corticosteroids.

### Antibiotics

Until some years ago, intestinal bacteria were considered one of the etiological factors in the pathogenesis of CD [23]. Considering this hypothesis, the efficacy of antibiotics has been investigated for the treatment of active CD. Furthermore, recent evidence has supported the immunodeficiency hypothesis, which suggests that bowel inflammation results from a failure of the way in which the body responds to the penetration of bacteria in the GI tract [24]. Based on this more recent evidence, the use of antibiotics in addition to immunomodulators in the treatment of CD should be validated.

A trial on the efficacy of ciprofloxacin underlined the efficacy of this antibiotic after 6 months of therapy [25]. Another study investigates the efficacy of ciprofloxacin (1 g daily) compared with 5-ASA in mild-to-moderate CD. Complete remission was observed in 56% of patients treated with ciprofloxacin and 55% of patients treated with 5-ASA (4 g daily). The authors concluded that ciprofloxacin is as effective as 5-ASA in treating mild-to-moderate flare-up of CD [26]. The efficacy of combination therapy with clarithromycin, rifabutin and clofazimine in addition to a course of prednisolone was compared with placebo therapy in patients with active CD [27]. After 16 weeks more patients achieved remission in the antibiotic arm compared with placebo arm. In an Italian study, treatment with rifaximin (800 mg twice daily) was found to be more effective than placebo in a subgroup of patients with active CD and elevated C-reactive protein values [28].

Several meta-analyses have been performed on the efficacy of different antibiotics, either alone or in combination. A meta-analysis on six small trials concluded that broad-spectrum antibiotics improve clinical outcomes in patients with CD [29]. Another meta-analysis included studies in which the efficacies of clofazimine, rifampicin, ethambutol, dapsone, isoniazid, sulphadoxine, pyrimethamine and rifabutin were evaluated [30]. The meta-analysis showed that these antimycobacterial therapies are not effective in CD without previous treatment with corticosteroids to induce remission. A meta-analysis evaluated the efficacy of nitroimidazoles and clofazime in active CD, showing the efficacy of both antibiotics [31]. In a more recent meta-analysis, a higher efficacy of antibiotics (antimycobacterial therapy, macrolides, chinolones, 5-nitroimidazoles and rifaximin) was reported compared with placebo, but with significant heterogeneity among the studies [32]. Another recent meta-analysis did not find any benefit of antibiotic treatment, compared with placebo [33]. However, the high heterogeneity of the included trials, the variable duration of the treatment and the different dosages used represent limitations of these meta-analyses.

With regard to antimycobacterial therapy, Greenstein *et al.* hypothesized that clinical improvement in patients with inflammatory bowel disease treated with methotrexate (MTX) and 6-mercaptopurine (6-MP) could be due to treating a *Mycobacterium avium paratuberculosis* (MAP) infection [34]. The authors showed that MTX and 6-MP inhibit MAP growth *in vitro* and in clinical studies evaluating the effect of anti-MAP agents, concluded that the concomitant use of MTX and 6-MP should be excluded. More recently, Bach *et al.* reported a harmful effect of infliximab on the survival of MAP [35]. On the other hand, some authors assumed that the immunomodulatory activity, rather than the anti-infectious effect of some antibiotics such as metronidazole, might explain the beneficial effects observed in the treatment of CD [31].

Based on all these discordant data, the use of antibiotics in CD is,to date, limited. In the ECCO guidelines, metronidazole and ciprofloxacin are not indicated in active disease, only in the presence of septic complications of CD or perianal disease [7].

### Thiopurines (AZA/6-MP)

The efficacy of thiopurines in active CD is controversial. A meta-analysis evaluating eight trials showed a higher response rate in patients treated with thiopurines compared with patients treated with placebo [8]. The

minimum period for an adequate response was found to be 17 weeks. The evidence of this slow onset of action precludes the use of thiopurines as a single therapy for active CD. Its use is only recommended in combination with corticosteroids [7]. In a more recent meta-analysis including five trials, no significant efficacy of thiopurines was observed in active CD [36]. The reason for this discrepancy between the results of the two meta-analyses is in the inclusion criteria of the trials. In the meta-analysis by Khan *et al.*, all trials evaluating patients after more than 17 weeks were excluded [36]. This discrepancy may indicate that a longer time of treatment gives a greater chance of obtaining a positive result. This is not very useful from the clinical point of view because in active disease you need to have a rapid response, which now is obtainable with biologics.

The efficacy of AZA/6-MP was compared with another drug in five trials: MTX [37], mycophenolate [38], everolimus [39], and biologics [40,41]. AZA/6-MP was found to be slightly less effective than MTX and mycophenolate, more effective than everolimus and more effective if associated to infliximab than alone. The population was made up of steroid-dependent patients in only three of these trials [37,40,41]. However, the rate of response to AZA, evaluable only in two studies [40,41], was 29–30%, which is clearly different from the results of the trial by Ewe *et al.*, where a remission rate of 76% was observed [42]. The heterogeneity of the population and the small number of samples do not allow the drawing of definitive conclusions on the role of AZA in inducing remission in CD.

Most of the trials have been carried out with AZA, but it is important to underline that in case of intolerance to AZA, a test with 6-MP is recommended because half of patients can tolerate a switch from one thiopurine to the other. A study evaluating the long-term outcomes of 6-MP treatment in patients with AZA intolerance showed that 52% of patients intolerant to AZA tolerated 6-MP [43].

### Methotrexate

Based on three small studies where the efficacy of low doses of oral MTX has been evaluated, MTX was found to be ineffective in the treatment of active CD [37,44,45]. In one of these studies MTX was compared with placebo [44], in the other two it was compared with placebo or 6-MP [37,45]. In addition, a small study where the efficacy of a higher dose of intravenous/oral MTX was evaluated, comparing it with AZA, showed no significant difference between MTX and AZA in this setting [46]. However, a more rapid effect of MTX in inducing remission compared with AZA was observed. Only a placebo-controlled trial supported the efficacy of a higher dose of intramuscular MTX (25 mg once weekly) in active CD compared with placebo [47]. However, a higher rate of adverse effects has been reported in treated patients compared with control arm.

A recent study compared the ability to assess the mucosal healing in patients with CD of MTX, AZA and infliximab [48]. Mucosal healing was less frequently achieved with MTX (11%) compared with AZA (50%) or IFX (60%). This result is very different from that reported in the SONIC study, where the rate of mucosal healing was 16.5% with AZA and 30% with infliximab monotherapy [40]. However, this study was not a controlled trial, therefore the results should be taken with caution. To date, on the basis of these results, MTX is considered to be an alternative drug for patients with active CD who are refractory or intolerant to thiopurines [7].

### Biologics

Anti-TNF-α molecules (infliximab, adalimumab and certolizumab pegol) have been widely used in the last 15 years for the treatment of active CD [49]. The efficacy of these drugs as induction therapy has been established in several trials and meta-analyses [50,51]. To date, infliximab and adalimumab have been approved for use in CD in many countries, while certolizumab pegol is not approved in the EU.

A comparison between infliximab and thiopurines has been carried out in two studies [40,41]. One study underlined the role of infliximab as induction treatment in steroid-dependent CD [41]. In this subgroup of patients, treatment with infliximab plus thiopurines was found to be more effective than thiopurines alone. The advantage of combination therapy with infliximab and thiopurines has also been investigated in the SONIC study [40]. In this trial, patients with moderate-to-severe CD were assigned to receive infliximab, AZA or a combination therapy with the two drugs. At week 26, 56.8% of patients treated with combination therapy were in steroid-free remission, compared with 44.4% of patients

treated with infliximab alone and 30% of patients treated with AZA alone. The authors concluded that in patients with moderate-to-severe CD, treatment with infliximab plus AZA or infliximab alone is more effective than a treatment with AZA alone. However, in this study the advantage of combination therapy was only evident in patients with normal CRP levels and absence of endoscopic lesions at baseline. Considering this particular result, the data from this trial are considered to be questionable.

Two meta-analyses confirmed the efficacy of biologic therapy in active CD [50,51]. However, the second meta-analysis confirmed the efficacy of infliximab and certolizumab pegol, but no significant difference was seen between certolizumab pegol and placebo groups in terms of clinical remission [51]. To date, no trials comparing the different anti-TNFα agents has been performed.

One limitation of the use of biologic therapy instead of other conventional drugs is the safety profile. Thus, the benefits of starting anti-TNF-α therapy should be balanced with the potential risks. Latent tuberculosis or other infections, severe heart failure, a history of demyelinating disease, an abdominal or perianal abscess, and a history of lymphoma must be considered absolute contraindications to anti-TNF-α therapy. Particular attention is necessary in older patients, who seem to have a higher rate of severe infections and mortality if treated with anti-TNF-α agents [52]. Recently, a higher risk of hepatosplenic T-cell lymphoma was observed in patients with inflammatory bowel disease treated with biologics combined with immunosuppressants. This type of lymphoma is a rare, lethal disease no longer restricted to the previously identified risk group of young male patients, but in recent times also reported in women and older adults receiving TNF-α inhibitors and immunomodulators [53].

## Quiescent CD

Most of the studies on maintenance treatment compared a single drug with placebo. Few studies have been published on comparisons between different drugs (Table 2). Steroids have been compared with AZA and SASP [9], and AZA has been compared with other immunosuppressants and with biologics [40]. In many of these trials the comparison has been carried out in an induction phase followed by a maintenance phase.

**Table 2. Trials comparing treatments in quiescent Crohn's disease.**

| Study (year) | Compared treatments | Most effective treatment | Ref. |
|---|---|---|---|
| Summers *et al.* (NCCDS) (1979) | Prednisone/SASP/AZA | No effective treatment | [9] |
| Oren *et al.* (1997) | MTX/6-MP | MTX | [37] |
| Mate-Jimenez *et al.* (2000) | MTX/6-MP | MTX | [45] |
| Mantzaris *et al.* (2009) | Budesonide/AZA | AZA | [60] |
| Feagan *et al.* (2008) | MTX + infliximab/infliximab | Infliximab | [65] |
| Colombel *et al.* (SONIC) (2010) | Infliximab/AZA/ infliximab + AZA | Infliximab + AZA | [40] |

6-MP: 6-Mercaptopurine; AZA: Azathioprine; MTX: Methotrexate; SASP: Sulfasalazine.

According to the ECCO guidelines, once remission has been obtained immunosuppressive treatment with thiopurines should be considered, especially if remission has been achieved with systemic corticosteroids and in the case of extensive disease [7]. MTX may also be considered in the case of patients who are refractory or intolerant to thiopurines. Immunosuppressants must be particularly considered in steroid-dependent CD to induce early steroid sparing. Corticosteroids (including budesonide) should not be used to maintain remission, as they cease to be effective and their long-term use is associated with many side effects. There is no reliable evidence for the efficacy of aminosalicylates in quiescent CD. In patients who relapse during treatment with thiopurines or MTX, a change of maintenance therapy to anti-TNF-α should be considered. If remission has been achieved with an anti-TNF-α agent, maintenance with the same therapy should be considered. In this case, thiopurines may be considered an option if the patient is naive to thiopurines.

### ■ Aminosalicylates

The efficacy of 5-ASA in maintaining remission has been evaluated in four meta-analyses published in different periods that all agreed on inefficacy of this drug [54–56]. No controlled trial has been carried out on the comparison between 5-ASA and other drugs such as AZA and MTX.

### ■ Corticosteroids

Considering the negative results of early studies [9,10] and their long-term toxicity, corticosteroids are not recommended in quiescent CD [7].

Long-term treatment with steroids has been compared with other drugs in only one trial. In 1979, the NCCDS evaluated the efficacy of prednisone, SASP and AZA in induction and maintenance treatment of CD. Regarding the maintenance phase, patients who had achieved remission after 17 weeks of therapy were maintained on the therapy that induced remission, including placebo, and followed for up to 24 months. At the end of the study none of the evaluated drugs were superior to placebo in maintaining remission. In a meta-analysis, the use of conventional corticosteroids in quiescent CD was not found to reduce the risk of relapse over a 24-month period of follow-up [57].

Together with these negative results, it is important to underline the high rate of side effects related to long-term treatment with corticosteroids. The occurrence of diabetes mellitus, hypertension, osteoporosis, acne, cataracts, glaucoma and the increased risk of infections, may worsen the outcome in these patients. The corticosteroid response is of particular importance in children with CD because the consequences of failed or long-standing therapy can be severe in these patients. Considering their toxicity, the use of corticosteroids should be avoided in pediatric patients and other treatments, such as short-term exclusive enteral nutrition and immunosuppressants, must be considered [58].

### Budesonide

Due to its topical anti-inflammatory activity and low systemic effect, the use of budesonide as maintenance treatment in CD has been proposed. The efficacy of budesonide in quiescent CD was analyzed in trials where budesonide at a dosage of 6 or 3 mg daily was compared with placebo, 5-ASA or conventional corticosteroids. In a meta-analysis including eleven of these trials, budesonide (6 mg daily) was found to be no more effective than placebo or prednisolone for the maintenance of remission at 12 months, but more effective than 5-ASA [59]. Budesonide (3 mg daily) was found to be more effective than placebo at 3 months, but not at 6 and 12 months. No influence was observed of different formulations of budesonide, method of induction of remission (medical or surgical) or drug dosage on treatment efficacy. The rate of adverse events was higher in patients treated with 6 mg daily of budesonide, but not in patients treated with lower doses. The authors concluded that budesonide cannot be recommended as maintenance treatment in CD.

A trial compared the efficacy of 1-year treatment with budesonide and AZA in patients with steroid-dependent CD. At the end of the study, AZA was found to be more effective than budesonide in maintaining clinical remission and inducing mucosal healing [60].

### Antibiotics

Different trials and meta-analyses have evaluated the efficacy of long-term antibiotic treatment in patients with CD. In the meta-analysis by Borgaonkar *et al.*, antimycobacterial therapy was shown to be effective in quiescent CD, but a small number of studies were included in this review [30]. In a following trial, combination therapy with either triple anti-tubercular therapy (clarithromycin, rifabutin and clofazimine) was evaluated, but no benefit of this therapy was observed after 2 years [27].

In a more recent meta-analysis, 16 trials evaluating the efficacy of different antibiotic treatments were analyzed [31]. Three trials of nitroimidazoles showed their benefit. No benefit was shown for anti-tuberculosis drugs. Another recent meta-analysis showed a significant efficacy of different antibiotic combinations (including antimycobacterials) in quiescent CD [32].

Despite the attempts of many authors to clarify the role of antibiotics in CD, the maintenance trials with antibiotics are characterized by poor methodology.

### Thiopurines (AZA 6-MP)

A few years ago, a meta-analysis including seven trials evaluated the efficacy of thiopurine as maintenance therapy in CD [61]. Thiopurines were found to have a positive effect on maintaining remission, but higher doses of AZA (2.5 mg/kg daily) were shown to be more effective than lower doses. A more recent meta-analysis confirmed the efficacy of thiopurines in quiescent CD [36]. However, the analysis of the studies on thiopurines does not seem to show them to be more effective than placebo. This result may be due to the negative conclusions of the study of Summers *et al.*, where a lower dose of AZA (1 rather than 2.5 mg/kg) was used [9]. A dosage of 2–2.5 mg/kg daily seems to be the adequate dosage to obtain a clinical result. Another meta-analysis investigated the question of how long treatment with thiopurines should

be continued [62]. Stopping thiopurine treatment was found to increase the risk of relapse at 6, 12 and 18 months. A clear benefit of continuing thiopurines for at least 18 months was observed.

Thiopurines have been evaluated in comparison with other drugs in the NCCDS, but the short period of comparison did not allow a valid conclusion [9]. In two studies 6-MP was compared with MTX [37,45]. In the first study MTX, at a weekly oral dose of 12.5 mg, was found to be moderately more effective than 6-MP in patients with chronic active CD [37]. In the second study, a statistical difference was observed between the maintenance remission rates in patients treated with 1.5 mg/kg daily of 6-MP (53.3%) and patients treated with 15 mg/week of MTX (66.6%) [45]. A Cochrane meta-analysis showed no difference between the two drugs [63].

### ■ Methotrexate

Over 10 years ago the efficacy of MTX in quiescent CD was established in the only available placebo-controlled trial [64]. In this trial, the effect was shown in patients who responded to MTX in acute phases. More recently, the efficacy of infliximab plus MTX compared with infliximab alone was evaluated in a trial [65]. After 50 weeks the concomitant treatment with infliximab and MTX was found to be no better than infliximab alone. The comparison with AZA has been previously discussed in the 'Thiopurines' section.

### ■ Biologics

Anti-TNF-α therapy is effective for the maintenance of remission in patients with CD who have a clinical response to induction therapy with biologics [7]. In two meta-analyses, anti-TNF-α agents were confirmed to be more effective than placebo for maintaining remission in CD [50,51]. In the SONIC study, the rate of maintaining remission was higher in patients receiving combined therapy with infliximab and AZA than in patients receiving infliximab or AZA alone, even after 50 weeks (46.2, 34.9 and 24.1%, respectively) [40]. However, to date the opportunity to use a long-term combined therapy is still debated because of the evidence of increased toxicity, in particular the recent emergence of hepatosplenic T-cell lymphomas [53].

With regard to the duration of treatment, there is evidence that adalimumab is able to maintain remission for up to 2 years in patients who responded to induction therapy [66] and that long-term infliximab treatment has a good safety profile [67]. However, no recommendation can be given for the duration of treatment with anti-TNF-α agents [7].

**Table 3. Trials comparing treatments in post-surgical Crohn's disease.**

| Study (year) | Comparing treatments | More effective treatment | Ref. |
|---|---|---|---|
| D'Haens *et al.* (2008) | AZA + metronidazole/ metronidazole | AZA + metronidazole | [76] |
| Ardizzone *et al.* (2004) | 5-ASA/AZA | AZA | [83] |
| Hanauer *et al.* (2004) | 5-ASA/6-MP | 6-MP | [84] |
| Reinish *et al.* (2010) | 5-ASA/AZA | AZA | [86] |
| Sorrentino *et al.* (2007) | Infliximab + MTX/5-ASA | Infliximab + MTX | [88] |
| Yamamoto *et al.* (2009) | Infliximab/AZA/5-ASA | Infliximab | [89] |

5-ASA: 5-Aminosalicylic acid; 6-MP: 6-Mercaptopurine; AZA: Azathioprine; MTX: Methotrexate.

## Prevention of postsurgical recurrence

The efficacy of many drugs has been investigated in comparison with placebo to decrease the risk of endoscopic or clinical recurrence in patients with CD after resection surgery. Few randomized trials have been carried out to compare different drugs (Table 3).

Aminosalicylates are the drugs more largely evaluated and their efficacy for preventing both clinical and endoscopic recurrence has been established, but with a small absolute benefit. Thus their role in this setting is, to date, questionable. Nitroimidazole antibiotics were found to be effective, but their use as a long-term treatment is limited by the occurrence of adverse effects. The role of thiopurines is controversial. Preliminary data also support the efficacy of infliximab in this subgroup of CD patients.

### ■ Aminosalicylates

Eight trials compared the efficacy of 5-ASA to that of placebo or other drugs in preventing postoperative recurrence. The results of these studies have been pooled in several meta-analyses. One meta-analysis showed a reduction in postoperative recurrence rates in patients treated with 5-ASA compared with patients treated with placebo [55]. Most benefit was observed in patients with ileitis and prolonged disease duration. In a more recent meta-analysis, 5-ASA was confirmed to be associated with a significantly reduced risk of clinical and endoscopic recurrence

when compared with placebo [68]. However, when 5-ASA was compared with thiopurines the difference was not significant. Even if in these meta-analyses aminosalicylates were found to be more effective than placebo for preventing clinical and endoscopic recurrence, the benefit was small with a difference in risk of approximately 10%. In addiction, the results from an Italian retrospective study showed that the probability of clinical and surgical recurrence within 10 years was not found to be different in patients receiving and not receiving 5-ASA prophylaxis [69].

One study evaluated whether a higher dosage of 5-ASA (4 g daily) may offer a therapeutic advantage over the standard dosage (2.4 g daily) in the prevention of postoperative recurrence. The authors concluded that a higher regimen of 5-ASA does not offer a clinically significant advantage in the prevention of recurrence after 1 year of follow-up [70].

Comparisons with AZA have been carried out and will be discussed in the 'Thiopurines' section. Based on these results, the role of aminosalicylates in preventing postoperative recurrence remains debatable.

### Budesonide

The efficacy of budesonide in preventing postoperative recurrence was evaluated in two trials [71,72]. In the first study, patients were treated with budesonide 6 mg daily or placebo for 12 months [71]. In the second study, patients were treated with budesonide 3 mg daily or placebo for 1 year [72]. In both studies, a high withdrawal rate was observed. Analyzing the results of the two studies, neither the endoscopic recurrence rate nor the clinical recurrence rate were reduced in patients treated with budesonide [73].

### Antibiotics

A trial evaluated the efficacy of metronidazole (20 mg/kg) in a postsurgical setting, comparing it with placebo [74]. In another study, the efficacy of ornidazole (1 g daily) was investigated [75]. A meta-analysis of these studies showed that the relative risk of clinical recurrence at 1 year and endoscopic recurrence at 3 months were reduced in the treatment group compared with placebo group [68]. However, the relative risk of clinical recurrence was no longer significant if only metronidazole was used. A study examined the effect of AZA given in combination with a 3-month course of metronidazole. The combination of AZA and metronidazole was reported to be more effective than the antibiotic alone in preventing endoscopic recurrence at month 12 [76]. Furthermore, antibiotic treatment was found to be associated with a higher risk of serious adverse events.

### Probiotics

Five studies evaluated the efficacy of different probiotics in preventing postsurgical recurrence [77–81]. None of these studies demonstrated the efficacy of probiotics in this setting. In a meta-analysis, probiotics were not shown to be superior to placebo for preventing clinical and endoscopic recurrence [68].

### Thiopurines (AZA/6-MP)

Four trials evaluating the efficacy of thiopurines in preventing postsurgical recurrence have been included in a meta-analysis [68]. The analysis of the studies where thiopurines were compared with placebo showed a reduced risk of clinical and endoscopic recurrence at 12 months in patients treated with thiopurines. When the efficacy of thiopurines was compared with that of 5-ASA, no difference could be detected between the two drugs. However, a lower risk of serious adverse events was reported with 5-ASA than with thiopurines. In another meta-analysis, thiopurines were reported to be more effective than control arms in preventing clinical and severe endoscopic recurrence at 1 year and clinical recurrence at 2 years [82]. The meta-analyses on the role of AZA in the prevention of clinical recurrence do not allow definitive conclusions to be drawn. In the meta-analysis by Peyrin-Biroulet *et al.*, four trials have been included with relevant heterogeneity (different populations, different dosages and different comparisons of drugs) [82]. The trial of Ardizzone *et al.* included patients who had undergone conservative surgical treatment (strictureplasty) [83]. In the trial by Hanauer *et al.*, 6-MP was under dosed [84]. In the trial by D'Haens *et al.*, metronidazole was given to all the patients [76] and in the trial by Herfarth the

**Table 4. Trials comparing treatments in fistulizing Crohn's disease.**

| Study (year) | Compared treatments | Most effective treatment | Ref. |
|---|---|---|---|
| Thia *et al.* (2009) | Ciprofloxacin/metronidazole | No significant difference | [96] |
| West *et al.* (2004) | Infliximab + ciprofloxacin/ infliximab | Infliximab + ciprofloxacin | [97] |

comparative drug was 5-ASA [85]. Analyzing the comparison with 5-ASA, a difference between the two treatments was not observed. However, looking at the results of the different studies we have contrasting results. In the studies by Hanauer *et al*. and Ardizzone *et al*. a comparison between the efficacy of thiopurines and 5-ASA was performed [83,84]. In the first study, a benefit for 6-MP versus placebo and a trend for 5-ASA versus placebo was observed in terms of clinical recurrence. A trend towards benefit with 6-MP, but not with 5-ASA, versus placebo was also reported in terms of endoscopic recurrence. In the second study, AZA was reported to be more effective than 5-ASA in patients who had undergone previous intestinal resection, while no difference between the two drugs was observed after conservative surgery.

Recently, a trial was conducted to compare AZA (2.0–2.5 mg/kg daily) and 5-ASA (4 g daily) for the prevention of clinical recurrence in patients with evident endoscopic recurrence [86]. After 1 year clinical recurrence was less frequent with AZA than with 5-ASA; however, study drug discontinuation, due to adverse drug reactions, only occurred in AZA-treated patients.

### ■ Biologics

In a small study evaluating the efficacy of infliximab in preventing postsurgical recurrence, the risk of endoscopic recurrence at 1 year was reported to be lower in patients treated with infliximab than in patients treated with placebo [87]. However, no more patients were in clinical remission in the infliximab group, compared with the placebo group. Similar results have been reported in a small uncontrolled series [88]. In this study, infliximab and low-dose MTX were administered 2 weeks after surgery, and compared with 5-ASA. After 2 years of follow-up no one in the group treated with infliximab and MTX demonstrated endoscopic or clinical recurrence. In the group treated with 5-ASA, only 25% of patients were disease free 2 years after surgery. In a prospective study, the efficacy of infliximab in the postsurgical setting was compared with 5-ASA and AZA [89]. Patients in clinical remission on 5-ASA, but with evidence of endoscopic recurrence 5 months after surgery, were assigned to 5-ASA (3 g daily), AZA (50 mg daily) or infliximab (8 weekly, without induction doses) treatment. After 6 months a clinical recurrence was reported in none of the patients treated with infliximab, in three patients treated with AZA (38%) and in seven patients treated with 5-ASA (70%). An endoscopic improvement was observed in 75% of the patients treated with infliximab, in 38% of the patients treated with AZA and in none of the patients treated with 5-ASA.

A small trial evaluated the efficacy and safety of IL-10 (Tenovil™) for preventing endoscopic recurrence at 12 weeks [90]. At the end of the study, an efficacy of this drug was not observed.

## Fistulizing CD

The treatment of fistulizing CD is very difficult, especially in case of perianal fistulas. In this case, achieving healing is a long process and recurrence is frequent after surgical treatment [91]. The efficacy of many medical treatments, alone or in combination with surgical procedures, has been evaluated in this subgroup of CD patients. Based on the Italian guidelines, in the case of complex fistulas 'cone-like' fistulectomy should first be performed and seton placement is recommended [92]. After surgical intervention, biologics represent the first choice of medical therapy. Antibiotics and immunosuppressants should be considered as second-line medical treatments. In the presence of a simple fistula, antibiotics are considered to be the treatment of choice, accompanied by surgical drainage. Use of drainage is still recommended considering that at the base of a fistula there is often an underlying abscess.

### ■ Antibiotics

Antibiotics (metronidazole and ciprofloxacin) have been proposed for the treatment of fistulizing CD for both their antiseptic and anti-inflammatory properties. Most evidence for the efficacy of antibiotics in fistulizing CD comes from uncontrolled case series involving few patients [93–95]. In these studies, a reduction in fistula drainage has been observed in patients receiving metronidazole at doses of 750–1000 mg daily or ciprofloxacin at a dose of 1000–1500 mg daily. Improvement is usually seen after 6–8 weeks of treatment, but fistulas generally re-occur after medical discontinuation. In a small trial, the efficacy of ciprofloxacin and metronidazole was compared [96]. Patients were randomized to receive ciprofloxacin, metronidazole or placebo for 10 weeks. The closure of all fistulas at week 10 occurred in three patients (30%)

treated with ciprofloxacin, no patients (0%) treated with metronidazole and one patient (12.5%) treated with placebo. This small study suggested that fistula remission occurred more often in patients treated with ciprofloxacin, but the difference was not significant. However, a recent meta-analysis concluded that there is a significant effect of these drugs on reducing fistula drainage [31]. Another trial evaluated the efficacy of combined ciprofloxacin and infliximab treatment in perianal CD [97]. A higher response rate was observed in patients treated with ciprofloxacin and infliximab compared with patients treated with infliximab alone. In addition, in fistulizing CD a limitation to the long-term treatment with antibiotics is the incidence of adverse events.

### ■ Thiopurines (AZA/6-MP)

No controlled trials have considered the efficacy of thiopurines as a primary end point in fistulizing CD and the studies where fistula closure was considered a secondary end point have small sample sizes. Thus a meta-analysis of these studies was conducted to produce a more reliable result on the efficacy of thiopurines in the treatment of perinal CD [98]. In this meta-analysis, which included five studies with 70 patients overall, a high rate of patients receiving thiopurines responded compared with patients receiving placebo. On the basis of this evidence thiopurines are considered a therapeutic option in the presence of perianal fistula.

### ■ Biologics

Infliximab was the first drug proven to be effective for inducing and maintaining the closure of perianal fistulas. In the first published trial, three infusions of infliximab induced a complete closure in a higher rate of patients compared with placebo [99]. In the ACCENT II trial, the superiority of infliximab in maintaining the long-term healing of fistulas was observed [100].

The first data on the efficacy of adalimumab in the treatment of perianal CD come from a subgroup analysis of a large trial [101]. Complete fistula closure was achieved in a higher rate of adalimumab-treated patients compared with placebo-treated patients at week 26 and 56. Patients completing week 56 were then enrolled in an open-label extension study that showed that 90% of patients maintained fistula healing after 1 additional year of adalimumab therapy [102].

Data on the efficacy of certolizumab pegol in the treatment of fistulizing CD come from subgroup analysis of large trials. PRECISE I [103] and PRECISE II [104] trials evaluated the efficacy of certolizumab pegol in a subgroup of patients with fistulizing CD. These studies were not powered to show a difference in remission of fistula draining at the end of the trial. In a subgroup analysis of a recently published study, complete fistula closure was observed in 36% of patients at week 6 and in 55% of patients at week 26 [105]. These results are considered promising but are still not sufficient to consider certolizumab pegol a treatment of choice for fistulizing CD.

In recent years, the efficacy of a combined surgical and medical treatment has been proposed. Several small trials have shown that the combination of seton placement and infliximab is superior to seton placement or infliximab alone [106–111]. A better response, lower recurrence and longer time to recurrence rates were reported in patients who had a seton placed prior to infliximab infusions compared with patients receiving infliximab alone. Recently, a prospective Italian study was conducted to compare the efficacy of infliximab, surgery or a combination of surgery and infliximab [112]. The authors concluded that patients treated with surgery and infliximab experienced a shorter time to healing of fistulas and a longer mean time to relapse compared with those treated with infliximab or surgery alone. The questions of which is the best maintenance treatment in fistulizing CD after biologic therapy and what is the best time to stop the treatment remain unsolved.

## Conclusion & future perspective

In recent years, the therapy of CD has made significant progress, but we are still far from obtaining complete long-term remission in all patients. Some of the recent recommendations are still based on expert opinions and most trials included in the recent meta-analyses are more than 10 years old. In recent years, the diagnostic techniques and the outcomes evaluated have changed, thus it is questionable whether the old studies can be compared with recent ones. Comparison trials are still necessary to evaluate which is the best treatment in different settings. Furthermore, most of the traditional published

trials used the CDAI score to quantify the efficacy of drugs in CD. However, in patients with CD apparent symptomatic improvement does not always reflect an improvement of the pathologic disease process. Particularly in steroid-dependent patients, the CDAI value does not reflect the real disease activity because patients could be asymptomatic due to steroid use. A more reliable parameter for therapeutic efficacy, involving the evaluation of mucosa and deeper tissues, is warranted for future trials. Furthermore, in traditional trials on fistulizing CD, the evaluation of fistula healing has been performed using the application of gentle pressure in the fistula hole. However, it was recently observed that inflamed fistula tracks often persist, despite the apparent closure of external orifices. Based on this observation the best diagnostic instruments, such as radiological examination, are warranted in future trials.

Comparing the different treatments, the efficacy of which has been evaluated in the different settings of CD, we can conclude that:

- In mild active ileocecal CD, budesonide is the treatment of choice;
- In mild colonic CD, SASP may be a rational therapeutic option;
- In moderate-to-severe disease, steroids are the first choice;
- In steroid resistant patients, biologics are the first choice;
- Maintenance of remission is mainly based on immunosuppressive treatment;
- In the postsurgical setting, the medical approach is still debatable. The available data do not support the superiority of thiopurines compared with aminosalicylates and data on the efficacy of biologics are still insufficient. Some evidence supports the efficacy of combination therapy with AZA and metronidazole. The treatment of fistulizing CD is based on a combined medical and surgical approach. Antibiotics are considered effective for improving symptoms, but are not able to induce fistula closure. Biologics should be used as first choice medical therapy in the case of complex fistula;
- An early immunosuppressive therapy is currently recommended in patients at risk of a worse prognosis, such as extensive disease, severe proctitis and young age. The opportunity for combined therapy with immunosuppressants and biologics has recently been discussed. Combination therapy shows some therapeutic benefits but may induce an increased risk of opportunistic infection and malignancy, in particular hepatosplenic T-cell lymphomas, so its use must be evaluated case by case. Finally, in the case of limited ileal disease, severe colonic disease and stenosis, the surgical approach must be keep in count.

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*The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.*

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## Executive summary

- Crohn's disease (CD) is a chronic disorder, characterized by phases of remission and relapse, with a wide spectrum of patterns and different clinical courses, meaning it is not easy to find the best therapy for all patients.
- Comparison between the different drugs used for the treatment of CD is often difficult because of the heterogeneity of the disease, meaning many of the evidences come from comparison with placebo.
- In active CD, the treatment of choice is: budesonide in mild ileocecal disease, sulfasalazine in mild colonic disease, steroids in moderate-to-severe disease and biologics in the case of steroid resistance.
- In quiescent CD, the maintenance of remission is mainly based on immunosuppressive treatment. The efficacy of medical treatments in maintaining remission after surgical resection is not clear. The superiority of thiopurines compared with aminosalicylates is debatable and data on the efficacy of biologics are insufficient.
- Early immunosuppressive therapy is recommended for patients at risk of a worse prognosis such as those with extensive disease, severe proctitis and young age.
- In the case of perianal fistulizing CD, a combined medical and surgical approach is recommended. Antibiotics are able to improve symptoms but not to induce fistula closure. Biologics are considered to be the first choice therapy in the case of complex fistula.

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