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Review article: remission rates achievable by current therapies for inflammatory bowel disease

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Review article: remission rates achievable by current therapies for inflammatory bowel disease

Running head: remission rates in IBD

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Professor Marc Lémann died suddenly on 26 August 2010, during the final stages of preparing this manuscript.

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Summary

Background and Aim: To review remission rates with current medical treatments for inflammatory bowel disease (IBD).

Methods We searched MEDLINE (source PUBMED, 1966 to January, 2011).

Results Induction and maintenance of remission was observed in 20% (range, 9-29.5%) and 53% (range, 36.8-59.6%) of ulcerative colitis (UC) patients treated with oral 5-ASA derivatives. Induction of remission was noted in 52% (range, 48-58%) of Crohn's disease (CD) patients and 54% of UC patients treated with steroids in population-based cohorts. Maintenance of remission was reported in 71% (range, 56-95%) of CD patients on azathioprine over a 6 month to 2 year period and in 60% (range, 41.7-82.4%) in UC at one year or longer. Induction and maintenance of remission was noted in 39% (range, 19.3-66.7%) and 70% (range, 39-90%) of CD patients on methotrexate over a 40 week period. Induction of remission was reported in 32% (range, 25-48%), 26% (range, 18-36%) and 20% (range, 19-23%) of CD patients on infliximab, adalimumab and certolizumab pegol, respectively. The corresponding figures were 45% (range, 39-59%), 43% (range, 40-47%) and 47.9% at weeks 20-30 among initial responders. Induction of remission was observed in 33% (range, 27.5-38.8%) and 18.5% of UC patients on infliximab and adalimumab, respectively. Maintenance of remission was noted in 33% (range, 25.6-36.9%) of UC patients on infliximab at week 30. Approximately one-fifth of CD and UC patients treated with biologicals require intestinal resection after 2-5 years in referral-center studies.

Conclusion In the era of biologics, the proportion of patients not entering remission remains high.

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INTRODUCTION

The management of failed medical treatment for inflammatory bowel diseases (IBD) remains a challenge. Failed medical treatment can be defined as primary nonresponse or loss of response (absence of remission) in primary responders to a given drug regimen. Drug intolerance leading to drug discontinuation should be also part of the definition of failure. The ultimate goal should be remission.

In clinical practice the first step is to rule out symptoms not related to disease activity and intestinal inflammation. Notably, exclusion of mechanical problems (stricture, fistula, short bowel), undiagnosed infection (from abscesses to enteric infections, *Clostridium difficile,* parasites or tuberculosis); the assessement of malnutrition should be part of the management of failed medical treatment. Loss of response should be confirmed by using serum (C-reactive protein) and fecal (calprotectin, lactoferrin) markers, as well as radiologic (ultrasound, computed tomography, magnetic resonance imaging) and/or endoscopic evaluation. The therapeutic armentarium for IBD mainly comprises 5-aminosalicylates (5-ASA), steroids, ciclosporin, thiopurines, methotrexate, anti-tumor necrosis agents (anti-TNF) agents and, in the United States (US), natalizumab. In 2011, a step-up approach is recommended for most patients with IBD. In case of failure of medical treatments, surgery should be considered.

In this review we summarize available data remission for each drug class with a focus on results from randomized, controlled trials. We will then review the need for surgery in IBD in the era of biological agents.

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METHODS

We searched MEDLINE (source PUBMED, 1966 to January, 2011) using as search terms "remission", "5-aminosalicylic acid ", "corticosteroids", "azathioprine", "6-mercaptopurine", "methotrexate ", "infliximab", "adalimumab", "certolizumab", "Crohn disease", "ulcerative colitis". For Crohn's disease (CD), clinical remission was defined as a Crohn's disease activity index (CDAI) < 150, while the definition of remission could vary among studies in ulcerative colitis (UC).

Defining failed medical treatment

There is increasing acceptance that induction of remission and its maintenance are the only really satisfactory markers of successful treatment. Definitions of partial response vary from one study to another and a partial response is usually of limited value to the patient.

Luminal Crohn's disease

Thia et al. recently demonstrated that clinical trial efficiency for induction studies in patients with mildly to moderately active Crohn's disease (CD) can be improved by using either a decrease of the CDAI by ≥70 points for the last two consecutive visits, or a decrease of the baseline CDAI by ≥100 points, as the primary end point for a trial[1]. However, the European Medicine Agency (EMA) recommended that the proportion of CD patients achieving remission (defined as a CDAI < 150) within the period of about 8 weeks is an appropriate primary end-point to justify short-term treatment of active CD; slowly-acting agents that require more than 8 weeks to demonstrate an effect should be considered as maintenance agents rather than induction agents[2].

Fistulizing Crohn's disease

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Sandborn et al. recommended that the primary endpoint for induction trials in patients with actively-draining enterocutaneous or perianal fistulas in CD be complete cessation of drainage from all fistulas[2]. More recently, the EMA stated that the primary end-point should be complete fistula closure at 8-12 weeks. According to EMA, magnetic resonance imaging is now recommended to demonstrate healing of fistulas.

Ulcerative colitis

After a comprehensive literature review, D'Haens proposed that the primary endpoint for therapeutic trials in UC should be induction of remission, defined as complete symptom resolution and endoscopic (mucosal) healing[3]. The same authors also concluded that induction trials should be 4 to 8 weeks in duration, being short enough on one hand to be clinically relevant in patients with active symptoms, but long enough on the other hand to allow sufficient time for mucosal healing to occur[3]. Similarly to CD, slowly-acting agents that require more than 8 weeks to demonstrate an effect should be considered as maintenance agents rather than induction agents[3].

Loss of response

Luminal Crohn's disease

In primary responders, the EMA recommended that the primary end-point should be the proportion of patients in whom clinical remission (CDAI < 150) is maintained and no surgery is needed thoughout at least 12 months.

Fistulizing Crohn's disease

The primary endpoint for maintenance trials should be defined as complete absence of drainage from all fistulas and the absence of any new or reopened fistulas or abscesses for at least 6 months[2].

Ulcerative colitis

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In primary responders, the goal of maintenance therapy in UC is to maintain steroid-free remission, defined both clinically and endoscopically[4]. In practice, the best way of defining remission may be a combination of clinical parameters (stool frequency ≤ 3/day with no bleeding) and normal or quiescent mucosa at endoscopy[4].

Drug intolerance

Overall, any adverse event that leads to drug withdrawal should be considered as a medical failure.

RESULTS

Failure to induce and maintain remission with available medications (Tables 1-4)

5-ASA

Crohn's disease

In mildly active localised ileocaecal CD, the benefit of mesalazine is limited and budesonide should be preferred to 5-ASA[5]. Active colonic CD may be treated with sulfasalazine if only mildly active[5]. 5-ASA preparations are not superior to placebo for the maintenance of remission in CD[6]. Overall, despite the use of oral mesalazine treatment in the past, new evidence suggests that this approach is minimally effective as compared with placebo and less effective than budesonide or conventional corticosteroids[7].

Left-sided and extensive ulcerative colitis

Overall, induction of global/clinical remission was observed in 20% (range, 9-29.5%) of patients treated with oral 5-ASA, and 7% of patients stopped 5-ASA for side effects[8]. Sulfasalazine was as effective as 5-ASA for induction of clinical remission, but was not as well tolerated as 5-ASA[8]. A six-week, multicentre, randomized, double-blind, controlled trial assessing the safety and clinical

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efficacy of a new dose (ASCEND I) of medication randomly assigned 301 adults with mildly to moderately active UC to delayed-release oral mesalamine 2.4 g/day (400 mg tablet [n=154]) or 4.8 g/day (800 mg tablet [n=147])[9]. Treatment success was not statistically different between the treatment groups at week 6. However, among the moderate disease subgroup, 57% of patients (53 of 93) given delayed-release oral mesalamine 2.4 g/day and 72% of patients (55 of 76) given 4.8 g/day achieved treatment success (P=0.0384)[9]. A randomised double blind study was performed in 127 ambulatory patients; all received 4 g/day (twice daily dosing) oral mesalazine for eight weeks and during the initial four weeks, they additionally received an enema at bedtime containing 1 g of mesalazine or placebo[10]. In patients with extensive mild/moderate active UC, the combination therapy was superior to oral therapy for improvement at 8 weeks[10, 11].

Overall, maintenance of clinical or endoscopic remission was observed in 53% (range, 36.8-59.6) of patients treated with oral 5-ASA, and 5.1% of patients stopped 5-ASA due to side effects[12]. Once-daily dosing of delayed-release mesalazine at doses of 1.6-2.4 g/day was as effective as twice-daily dosing for maintenance of clinical remission in patients with UC[13]. 5-ASA preparations had a statistically significant therapeutic inferiority relative to sulfasalazine for maintenance of clinical remission[12]. However, most of the trials comparing 5-ASA with sulfasalazine enrolled patients who were known to tolerate sulfasalazine. This may have reduced sulfasalazine-related side effects in these trials[12].

A new, oral delayed-release formulation of mesalazine utilizing Multi Matrix System (MMX) technology was recently approved in the US for the induction and maintenance of remission in patients with active, mild-to-moderate UC. It is a high dose (mesalazine 1.2 g/tablet), delayed-release form that permits once-daily administration[11]. Induction of remission rates ranged from 18% to 41.2% at week 8 and 67.8-72.3% of patients treated with MMX mesalazine maintained remission at 1 year[11].

Distal ulcerative colitis

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Symptomatic remission was achieved in 58.6% (range, 46.5-81.2%) of patients treated with rectal 5-ASA (suppositories, enemas or foam) for distal UC in randomized placebo-controlled trials[14]; neither total daily dose nor 5-ASA formulation affected treatment response. 5-ASA was significantly superior to rectal corticosteroid for induction of clinical remission. Sixty patients with active distal UC participated in a multicentre randomized double-blind trial to compare the effect of a beclomethasone dipropionate (BDP) enema (3 mg/100 ml) with 5-ASA enemas (2 g/ 100 ml) and enemas with a combination of BDP/5-ASA (3 mg/2 g/100 ml)[15]. The combination of BDP and 5-ASA was significantly superior to single-agent therapy in terms of both improved sigmoidoscopic and improved histological score[15]. A four-week, randomized, single-blind trial enrolled 58 patients with active, histologically confirmed ulcerative proctitis (< or = 15 cm) to evaluate the efficacy and safety of oral 800-mg mesalazine tablets taken three times per day (n = 29) compared with 400 mg of mesalazine suppositories administered three times per day (n = 29)[16]. Treatment with mesalazine suppositories produces earlier and significantly better results than oral mesalazine[16]. Sixty outpatients with active distal UC not more than 50 cm were randomized to either mesalamine rectal enema (n = 18) once nightly, oral mesalamine 2.4 g/day (n = 22), or a combination of both treatments (n = 20)[17]. The combination of oral and rectal mesalamine therapy produced earlier and more complete relief of rectal bleeding than oral or rectal therapy alone[17]. Overall, maintainenance of clinical or endoscopic remission was observed in 52-90% of patients receiving rectal 5-ASA[18].

Antibiotics

Crohn's disease

Long-term treatment with nitroimidazoles or clofazimine is effective for luminal CD[19, 20]. However, the risk of *C difficile* infection, the development of bacterial resistance to antibiotics over time and the side effects limit their long-term use[19]. Overall, antibiotics are mainly used in clinical practice in combination with immunosuppressive therapy in patients with perinal CD and to prevent postoperative recurrence in CD[21].

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Ulcerative colitis

Except in severe colitis for which efficacy of antibiotics remains debated, antibiotics are not effective for the treatment of UC[19].

Corticosteroid therapy

Oral steroids, including budesonide, are not more more effective than placebo to maintain clinical remission in IBD and should not be used in this indication[5, 7].

Crohn's disease

Two randomized, controlled clinical trials compared traditional, systemic corticosteroids for the induction of remission of active CD to placebo and six studies have compared corticosteroids to 5-ASA[22]. Corticosteroids were effective for induction of remission in CD, which was achieved in 60% (range, 47-83%) of patients when used for more than 15 weeks[22]. Interestingly, although corticosteroids cause more adverse events than either placebo or low-dose 5-ASA, these adverse events did not lead to increased study withdrawal in the included studies[22].

The efficacy of corticosteroid therapy was investigated specifically in two population-based studies[23, 24]: among 74 CD patients treated with systemic steroids, 43 (58%) were in complete remission (defined as total regression of clinical symptoms) after 30 days[23]; in an earlier population-based study from Denmark, complete remission (defined as total regression of clinical symptoms) was obtained in 48% of 109 patients[24].

Although short-term efficacy with budesonide is less than with conventional steroids, particularly in those with severe disease or more extensive colonic involvement, the likelihood of adverse events and adrenal suppression is lower[25]. Hence, for those patients with mild ileocaecal or proximal colonic disease, budesonide should be preferred to systemic steroids because of its favourable side-effect profile[5].

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Ulcerative colitis

In a population-based study from Olmsted County, US, 54% (34 of 63) UC patients treated with systemic steroids were in complete remission after 30 days[23].

Enteral nutrition in Crohn's disease

Corticosteroid therapy is more effective than enteral nutrition for inducing remission of CD[26]. Whether it is effective for maintenance of remission in CD will require larger studies[27]. Overall, there would seem no logical reason to choose enteral nutrition over steroids for the vast majority of adult CD patients[28]. The European Society for Parenteral and Enteral Nutrition published guidelines in 2006 on the use of enteral nutrition in gastroenterology[28]. They suggested that a role could be found for enteral nutrition in in the following circumstances: steroid intolerance, patient refusal of steroids, enteral nutrition in combination with steroids in undernourished individuals, and in patients with an inflammatory stenosis of the small intestine[28].

Thiopurines (azathioprine, mercaptopurine)

Crohn's disease

Maintenance of remission in randomized, placebo-controlled trials was obtained in 71% (range, 56-95%) of patients receiving 1-2.5 mg/kg/d azathioprine[29]; this rate was 51% (24/47) for 50 mg/d mercaptopurine[29]. The percentage of adverse effects possibly leading to drug withdrawal was observed in 6% of patients with azathioprine and 19.1% of patients receiving mercaptopurine during maintenance treatment[29].

Ulcerative colitis

Maintenance of clinical remission was observed in 41.7-82.4% of patients on a thiopurine [30]. In uncontrolled studies, azathioprine was effective in 66% (95% CI, 64–69%) of patients, while mercaptopurine was effective in 61% (95% CI, 56–66%) of the patients[30].

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Methotrexate

Crohn's disease

Induction of remission or possible remission ranged from 19.3% to 66.7% at 16 weeks in randomized placebo-controlled trials enrolling adult patients with refractory CD[31]. The percentage of withdrawal due to adverse effects ranged from 4 to 20% in the same trials[31]. In randomized placebo-controlled trials, 39-90% of patients maintained clinical remission[32]. While intramuscular methotrexate at a dose of 15 mg/week is safe and effective for maintenance of remission in CD, oral methotrexate (12.5 to 15 mg/week) does not appear to be effective for maintenance of remission in CD[32]. Subcutaneous administration may be as effective as intramuscular dosing[33], possibly leading to increased treatment adherence.

Ulcerative colitis

A single trial of methotrexate 12.5 mg orally weekly showed no benefit over placebo for the induction of remission in patients with active UC – that is, remission and complete withdrawal from steroids in 46.7% of patients in the active arm, compared to 48.6% in the placebo arm[34]. However, the possibility of a type 2 error exists, and a higher dose of methotrexate may be effective. Large randomized controlled trials are ongoing. In the same trial, 35.5% of patients maintained clinical remission. Withdrawal because of side effect was reported in 6.7% of patients treated with methotrexate[34]. The majority of uncontrolled retrospective analyses suggest a clinical response to methotrexate therapy in a range of 30%–80% when the drug is administered by a parenteral route in doses between 20–25 mg per week[35].

Primary response to anti-TNF agents

Crohn's disease

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In randomized controlled trials, clinical remission rates at week 4 were 25-48% for infliximab, 18-36% for adalimumab, and 19-23% for certolizumab pegol in luminal CD[36]. In randomized controlled trials evaluating maintenance of remission after open-label induction, clinical remission rates at weeks 20-30 were 39-59% for infliximab (Rutgeerts 1999 and ACCENT 1 trials), 40-47% for adalimumab (CHARM trial), and 47.9% for certolizumab pegol (Precise 2 trial) in luminal CD[36]. Steroid-free remission was reported in 12-16% of patients at weeks 48-52 for infliximab and 23-29% for adalimumab[36].

In short-term induction randomized controlled trials, complete fistula closure rates were 38-55% for infliximab, 0-75% for adalimumab. In maintenance trials with randomization after open-label induction, complete fistula closure rates were 34% for infliximab, 54% for certolizumab, and 30-37% for adalimumab[36]. In the short- and long-term induction trial PRECISE 1, complete fistula closure was 31% in the certolizumab group[36].

In a referral centre study, about 10% of CD patients were judged as primary non-responders to infliximab, 12.8% of patients stopped infliximab for side effects, and sustained clinical benefit was observed in 347 out of 614 (57%) patients who received at least one infliximab infusion[37].

Ulcerative colitis

In randomized, placebo-controlled trials, clinical remission rates at week 8 were 33% (range, 27.5-38.8%) for infliximab and 18.5% for adalimumab[38, 39]. Clinical remission was maintained in 33% (range, 25.6-36.9%) of patients treated with infliximab at week 30[38]. In a referral center study, about one-third of UC patients were judged as primary non-responders to infliximab, and sustained clinical benefit was observed in 55 out of 121 (45.5%) patients who received at least one infliximab infusion[40]. A systematic review on the efficacy of TNF antagonists beyond one year in both CD and UC concluded that we have no good reasons to stop anti-TNF therapy in IBD patients because of its efficacy in maintaining remission and a risk-benefit ratio that remains in its favor[41]. Infliximab

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therapy may be also effective in inducing and maintaining a clinical response in refractory ulcerative proctitis[42].

Loss of response to anti-TNF agents

The annual risk for loss of infliximab response was calculated to be 13% per patient-year in CD[43]. We found that the mean percentage of patients who lost response to adalimumab was 18.2% and the annual risk for loss of response was calculated to be 20.3% per patient-year in CD[44]. Hence, rates of loss of response to infliximab and adalimumab are broadly similar. In a French multicenter experience, infliximab optimization was required in 36 (45.0%) of 80 UC patients on scheduled infliximab therapy[45].

In the ACCENT 1 trial, among patients who lost response while in the 5 mg/kg scheduled treatment strategy group, approximately 90% re-established response after receiving 10 mg/kg[46]. In a single-center cohort in Leuven, Belgium, of 547 patients with CD, 66% (75/108) of those who shortened their dosing interval regained clinical response until the end of follow-up[37]. In the ACCENT 2 trial, among randomized patients with a response during maintenance therapy who subsequently lost their response because of a recrudescence of draining fistulas, 57 percent of patients (12 of 21) reestablished a response on crossing over from an infliximab dose of 5 mg per kilogram to a dose of 10 mg/kg[47]. Adalimumab induces clinical remission more frequently than placebo in CD patients who cannot tolerate infliximab or have symptoms despite receiving infliximab therapy[48, 49]. Response to a third anti-TNF therapy occurs in some patients and may be an appropriate option[5, 50]. Importantly, all anti-TNF agents have the potential for immunogenicity[51, 52]. A way to reduce immunogenicity and loss of response to anti-TNF therapy may be the use of concomitant immunomodulators. In the SONIC trial, of the 169 CD patients receiving combination therapy, 96 (56.8%) were in corticosteroid-free clinical remission at week 26 (the primary end point), as compared with 75 of 169 patients (44.4%) receiving infliximab alone (P=0.02)[53]. However, the risk-

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benefit of combination therapy should be assessed in lieu of recent reports of hepatosplenic T-cell lymphomas in young males receiving combination therapy[54] as well as the increased risk of opportunistic infections[55].

Others

There is no published randomized controlled trial on thalidomide for induction of remission in CD [56] and there is no evidence to support the use of thalidomide or its analogue, lenalidomide, as maintenance therapy in CD[57]. Furthermore, its long-term use is limited by toxicity[58]. Numerous treatments have been tested in IBD, including growth factors, hyperbaric oxygen, *Trichuris suis* ova, delayed release phospatidylcholine and leukocyte apheresis, but none of them has clearly shown its efficacy in these patients. In addition, off-label use should be discouraged. Accordingly, neither European nor North-American consensus proposed these therapeutic options for IBD refractory to conventional treatments[5, 7, 18, 59].

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Need for surgery in the era of biologics

Surgery should always be considered in case of failed medical treatment[5].

Crohn's disease

In luminal CD, in the ACCENT 1 trial, 11 out of 385 (3%) patients receiving combined scheduled infliximab therapy (5 or 10 mg/kg) required surgery throughout the 54-week trial compared with 14/188 (7.5%) in episodic strategy patients ((P = 0.01)[46]. In the CHARM trial, fewer major CD-related surgeries occurred in the combined adalimumab groups (3/517, 0.6%) compared with placebo (10/261, 3.8%; P = 0.005) at 1 year[60]. In fistulizing CD, the ACCENT 2 trial enrolling 282 patients showed that the 5 mg/kg infliximab maintenance group had an approximately 50% reduction in the mean number of all surgeries and procedures, compared with the placebo maintenance group: 60 vs. 118 and 65 vs. 126 surgeries and procedures per 100 patients, respectively, for all randomized patients (P=0.01) and patients randomized as responders (P=0.05)[61].

In a referral center study, 614 patients were treated with infliximab therapy between November 1994 and January 2007 for moderate to severe luminal CD. A total of 144 patients (23.5%) underwent major abdominal surgery after a median follow-up of 55 months[37]. The need for colectomy in CD remains poorly investigated in population-based studies. In Stockhom, Sweden, 33 out of 191 (17%) patients treated with infliximab for CD underwent major abdominal surgery after a mean number of 2.6 infusions[62]. In a population-based cohort from Cardiff (1986-2003), there was a significant reduction in the cumulative probability of intestinal surgery at 5 years from 59% (1986-1991) to 25% (1998-2003)[63].

Ulcerative colitis

The ACT-1 and -2 randomized, double-blind, placebo-controlled studies evaluated infliximab induction and maintenance therapy in moderate to severe active ulcerative colitis. Overall, 728

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patients received placebo or infliximab (5 or 10 mg/kg) intravenously at weeks 0, 2, and 6, then every 8 weeks through week 46 (ACT-1) or 22 (ACT-2). The cumulative incidence of colectomy through 54 weeks was 10% for infliximab and 17% for placebo (P = .02), yielding an absolute risk reduction of 7%[64]. A randomized double-blind trial of infliximab or placebo in severe to moderately severe UC not responding to corticosteroid treatment included 45 patients (24 infliximab and 21 placebo). Seven patients in the infliximab group and 14 in the placebo group had a colectomy (P =0.017; odds ratio, 4.9; 95% confidence interval, 1.4-17) within 3 months after randomization[65].

In Leuven, Belgium, among 121 patients treated with infliximab therapy for refractory ulcerative colitis, after a median follow-up period of 33.0 (17.0–49.8) months, 21 patients (17%) came to colectomy[40]. In a French multicenter experience, 36 patients (18.8%) underwent colectomy after a median follow-up per patient of 18 months[45]. Similarly to CD, the need for colectomy in UC remains poorly investigated in population-based studies. In Stockhom, Sweden, 8 out of 22 (36%) patients treated with infliximab for UC underwent colectomy after a mean number of 2.6 infusions[62]. Overall, between 10 and 36% of adult patients treated with infliximab for UC underwent colectomy in clinical trials, referral center studies and population-based cohorts[66].

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DISCUSSION

Only one-fifth of UC patients will enter remission on oral 5-ASA treatment. Historical population-based cohort studies demonstrated that about half of CD and UC patients will enter remission on systemic corticosteroids. About one third of IBD patients will maintain remission on thiopurines. Induction of remission is observed in only 2 to 3 out of 10 IBD patients treated with anti-TNF agents. In addition, less than half of IBD patients will maintain remission on anti-TNF therapy. Overall, in the era of biologics, approximately one-fifth of CD and UC patients treated with anti-TNF therapy require intestinal resection. The humanized interleukin-12/23 antibodies and vedolizumab (MLN002) appear to be the most promising biological agents for IBD[67, 68], but it may take several years before these molecules receive regulatory approval.

Given the lifelong course of these conditions and pending marketing approval for new drug classes, it is particularly important that each therapeutic agent be optimized before declaring treatment failure/loss of response and introducing an alternate (more potent and/or more toxic) therapy[69, 70]

Patients treated with anti-TNF therapy earlier rather than later in the disease course may achieve better treatment outcomes[71, 72]. In a referral center study from Nancy, France, noncomplicated inflammatory disease behaviour and long-term anti-TNF therapy were associated with a lower risk for surgery whereas azathioprine only modestly lowered this risk[73]. However, even though most experts agree that only top-down approaches may reduce the risk of medical failure, there is still no evidence in IBD that such therapeutic strategy can decrease the need for surgery when compared to step-up approaches[74].

The definition of new endpoints, such as complete mucosal healing in UC, prevention and reduction of bowel damage and disability in CD[71, 75], achieving deep remission (endoscopic and/or radiologic healing in addition to clinical and biological remission) may represent another way to alter the course of IBD using available medications and rapid step-up approaches. This remains to be

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investigated in large prospective disease-modification trials. There is no medical regimen or surgical strategy that provides a reliable cure for inflammatory bowel disease.

CONCLUSIONS

Steroid-free remission is the only really convincing endpoint for IBD therapies and, when judged by this endpoint, current therapies are seen still to fall some way short of what patients need. It is hoped that increasing emphasis on the importance of striving for mucosal healing and complete remission may encourage the development of more effective therapies.

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Table 1. Remission rates using medical treatments in ulcerative colitis in induction randomized, controlled trials.

	Overall rate: N (%)	Range (%)	Reference
Rectal 5-ASA	**293/500 (58.6%)**	**46.5-81.2%**	[14]
Oral 5-ASA	**124/622 (20%)**	**9-29.5%**	[8]
Systemic steroids in population-based cohorts	**34/63 (54%)**	**-**	[23]
Infliximab	**160/484 (33%)**	**27.5-38.8%**	[38]
Adalimumab	**24/130 (18.5%) for 160/80 mg induction regimen**	**-**	[36]

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Table 2. Remission rates using medical treatments in ulcerative colitis in maintenance randomized, controlled trials.

	Overall rate: N (%)	Range (%)	Reference
Oral 5-ASA	**254/480 (53%)**	**36.8-59.6%**	[12]
Thiopurines	**74/124 (60%)**	**41.7-82.4%**	[30]
Infliximab*	**160/484 (33%)**	**25.6-36.9%**	[38]

* When considering both initial responders and patients with primary non-response.

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Table 3. Remission rates using medical treatments in luminal Crohn's disease in induction randomized, controlled trials.

	Overall rate: N (%)	Range (%)	Reference
Systemic steroids in population-based cohorts	95/183 (52%)	48-58%	[23, 24]
Systemic steroids in randomized, controlled trials	79/132 (60%)	47-83%	[22]
Methotrexate	52/135 (39%)	19.3-66.7%	[31]
Infliximab	27/83 (32%) at week 4	25-48%	[36]
Adalimumab	58/225 (26%) at week 4	18-36%	[36]
Certolizumab pegol	109/550 (20%) at week 4	19-23%	[36]

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Table 4. Remission rates using medical treatments in luminal Crohn's disease in maintenance randomized, controlled trials.

	Overall rate: N (%)	Range (%)	Reference
Azathioprine	**147/208 (71%) over a 6 month to 2 year period**	**56-95%**	[29]
Methotrexate	**35/50 (70%) over a 40 week period**	**39-90%**	[32]
Infliximab*	**117/262 (45%) at weeks 20-30**	**39-59%**	[36]
Adalimumab*	**143/329 (43%) at weeks 20-30**	**40-47%**	[36]
Certolizumab pegol*	**103/215 (47.9%) at weeks 20-30**	**-**	[36]

* When considering only initial responders to anti-TNF therapy after open-label induction.

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