Top-down or step-up treatment in Crohn's disease?

Rogler, Gerhard

DOI: https://doi.org/10.1159/000347190

Intestinal Bowel Diseases

Digestive Diseases

Dig Dis 2013;31:83–90
DOI: 10.1159/000347190

Top-Down or Step-Up Treatment in Crohn's Disease?

Gerhard Rogler[a, b]

[a]Division of Gastroenterology and Hepatology, Department of Internal Medicine, University Hospital Zürich, and
[b]Zürich Center for Integrative Human Physiology, University of Zürich, Zürich, Switzerland

Key Words
Crohn's disease · Biologicals · Top-down approach · Step-up approach · Immunosuppression · Mucosal healing

Abstract
In recent years, a change in the treatment goals for patients with Crohn's disease (CD) has come under intense discussion. Whereas 10 years ago treatment was initiated mainly in reaction to acute flares of the disease aimed to improve clinical symptoms, the focus now has changed to the prevention of damage to the intestinal wall. The prevention of structural damage by achievement of 'mucosal healing', however, is associated with the more 'aggressive' treatment and an earlier use of immunosuppressants and biologicals. The use of immunosuppressants and biologicals especially in patients with CD has decreased the rates of surgery and hospitalizations, indicating that there is a group of patients definitely profiting from such an early use of immunosuppressive treatment. In this group of patients, the benefits outweigh the disadvantages of immunosuppression: the increased risk of severe infections. However, it remains questionable whether this improvement can only be achieved by completely reversing established treatment strategies. The dispute has been condensed to the questions whether 'top-down' (e.g. start with a combination of biological and immunosuppressant and 'de-escalate' if possible) or 'step-up' treatment (e.g. start with topical steroids, step up to systemic steroid, go to immunosuppression and biologicals if necessary) may be better. In general, in an upcoming era of individualized and personalized medicine, a 'one-size-fits-all' approach does not appear to be desirable. CD patients definitely should not be undertreated (which is still frequently the case) or remain on steroid treatment (which is inappropriate); however, overtreatment (putting patients at risk of side effects without benefit) is against a fundamental principle of medicine: nihil nocere (do no harm).

What Does 'Step Up' Mean for Crohn's Disease Therapy?

Usually the term 'step-up' treatment in Crohn's disease (CD) refers to a more traditional approach of therapy: for a newly diagnosed patient suffering from CD, first an approach is used that has a relatively lower risk of (severe) side effects. The choice of therapy is based on 'the balance between drug potency and potential side-effects; previous response to treatment … and the presence of

KARGER

E-Mail karger@karger.com
www.karger.com/ddi

0257–2753/13/0311–0083$38.00/0

Gerhard Rogler, MD, PhD
Division of Gastroenterology and Hepatology, University Hospital Zürich
Rämistrasse 100
CH–8091 Zürich (Switzerland)
E-Mail gerhard.rogler@usz.ch

extraintestinal manifestations or complications' as stated in the ECCO guidelines [1].

As obvious from Cochrane reviews and meta-analyses, the benefit of sulfasalazine and 5-aminosalicylic acid (5-ASA) preparations in uncomplicated CD is quite limited [2–4]. In a meta-analysis of three double-blind randomized studies on the role of 5-ASA in the treatment of active CD, 4 g/day 5-ASA was superior to placebo in reducing the Crohn's disease activity index (CDAI); however, the clinical effect was not convincing [4, 5]. Nevertheless, even new treatment guidelines still suggest to test a short course of sulfasalazine in colonic CD and not to exclude 5-ASA use in mild ileocecal disease ('the benefit of mesalazine is limited') [1]. In population-based studies, such as the IBSEN cohort, there is a significant amount of CD patients that only received treatment with 5-ASA and never needed steroids [6, 7]. Interpretation of those data is debatable.

There is better evidence for the use budesonide in mild-to-moderate flares of CD as the next step of treatment [1, 8–11]: 9 mg budesonide per day is effective and superior to treatment with 5-ASA [1, 8] for the induction of remission in CD patients. Budesonide will induce remission in 51–60% of the patients within 8–10 weeks [1, 8–11]. Mucosa healing is achieved in only 24% of treated patients [12]. The treatment is associated with limited side effects. Typical glucocorticoid-associated side effects are less frequent as compared to systemic glucocorticoid treatment [9, 11, 13–15]. In patients with high disease activity and/or combined disease location in the ileum and colon, 18 mg budesonide per day is more effective; however, systemic side effects become apparent more frequently [16].

In more severe disease, the next step up would be the administration of systemic glucocorticoids. By a prednisone/prednisolone treatment with 100 mg/day, remission can be achieved within 6 weeks in up to 92% of patients [17, 18].

In a systematic Cochrane review on the efficacy of conventional corticosteroids, the authors identified two studies that compared corticosteroids to placebo and six studies that compared corticosteroids to 5-ASA [18]. Corticosteroids were found to be significantly more effective than placebo at inducing remission in CD [18]. In short-term intervention with steroids, the number of adverse events did not differ between the glucocorticoids and high-dose 5-ASA [18]. Furthermore, glucocorticoids were not associated with more study withdrawals due to adverse events than placebo or 5-ASA [18]. This indicates that steroids are relatively safe and well tolerated for the treatment of acute flares of CD.

In a 'classical step-up approach' in patients not responding to steroids (steroid-refractory) or in which steroids cannot be tapered (steroid-dependent), immunosuppressants [azathioprine (AZA); 6-mercaptopurine (6-MP); methotrexate (MTX)] or biologics (infliximab, adalimumab, certolizumab pegol) may be used [1]. AZA (2–2.5 mg/kg body weight/day) and/or 6-MP (1.0–1.5 mg/kg body weight/day) have been shown to be effective immunosuppressants in inflammatory bowel disease (IBD) [19]. Near-complete mucosa healing has been reported in up to 83% of patients [12]. MTX is a suitable alternative (25 mg parenterally/once weekly) [20].

If a rapid treatment response is desired or if no remission can be achieved with AZA/6-MP/MTX, treatment with antibodies against TNF (infliximab, adalimumab, certolizumab) is associated with a success rate in up to 60–70% of the patients [21–25]. About 60% of the patients who respond initially will achieve long-term remission [26–29]. There is a certain rate of secondary loss of response that is similar for all anti-TNF products [30–35]. The different antibodies differ slightly in their therapeutic efficacy [36].

In contrast to studies that are based on single-center experience or data from large hospitals in population-based cohorts, around 50% of patients with CD are reported to have been treated with corticosteroids [37]. In a population-based cohort from Olmsted County, it was reported that more than one third of CD patients achieved remission with a treatment 'one step below' systemic glucocorticoids [37]. This indicates that a group of CD patients (which may usually not be seen at referral centers) requires only mild therapy. From several population-based cohorts (Olmstead County, IBSEN) it may be concluded that 30–50% of patients will require immunosuppression. Of those, about 50 or 15–25% of the total CD population will not be sufficiently treated with purine analogs [38, 39]. These patients will need to step up to anti-TNF therapy.

What Does 'Top Down' Mean in CD Therapy?

The term 'top down' in the context of CD therapy means that biologicals and immunosuppressants are applied right after the diagnosis of CD as a first-line therapy. The 'character' of the disease (whether it is mild disease with low activity and infrequent flares, aggressive disease with frequent flares, or chronic active inflammation) is not further evaluated as this would further require some weeks or months.

The rationale for such an approach comes from rheumatology where an early intervention with biologicals is thought to be 'disease-modifying', e.g. preventing progressive destruction of joints [40]. In reality, of course, not all rheumatologic patients are treated top down.

With the top-down approach, one important question remains: What can we do with the 40% of patients that don't come into remission as we know from the SONIC study [41] and other trials, the so-called 'primary nonresponders?' [27, 42]. The use of a second or even a third anti-TNF drug may eventually be effective [43, 44]; however, patients failing a first anti-TNF antibody are less likely to achieve remission with a second anti-TNF agent [44]. Another question that arises is how to maintain remission in those patients. In the STORI trial, a stopping strategy and criteria for therapy discontinuation have been provided [45]. In a prospective approach in 115 patients with CD that had been treated for at least 1 year with infliximab and thiopurines and had been in remission for more than 6 months, infliximab was stopped and thiopurine therapy maintained [45]. The relapse rate after 1 year was reported to be 44%. Risk factors for a relapse were increased leukocyte counts, decreased hemoglobin levels, increased CRP and fecal calprotectin, as well as absence of mucosal healing [45]. In the patients experiencing a relapse, retreatment with infliximab was effective in 88% [45].

Whereas it is now generally accepted that anti-TNF therapy should be administered on a regular basis ('scheduled treatment') as this reduces the risk for the formation of neutralizing antibodies, loss of response and allergic reactions unfortunately in the 'top-down – step-up' study by D'Haens et al. [46], infliximab was given more or less 'on demand' after induction therapy.

Unfortunately the 'step-up' and 'top-down' approach are frequently discussed as exclusive alternatives indicating that either the one or the other strategy should be followed. In contrast, it appears to be reasonable to identify a population that is at high risk of a severe and damaging disease course that will profit from a more aggressive approach with high probability. For those patients, the risk/benefit ratio certainly would indicate a benefit for 'top down' in the long run, whereas the risk/benefit ratio will have an imbalance to the risk side for a CD patient population with a mild disease course and low risk of complications. An additional negative impact on this discussion is that even in manuscripts that favor 'top-down' therapy only for such risk populations, general assumptions on CD are made (e.g. the conventional 'step-up' treatment approach does not alter the natural history of the disease, which obviously is wrong as the 'natural' history would be without intervention) that indicate an advantage of 'top-down' treatment for the whole CD patient population.

Table 1. Arguments for a top-down treatment in patients with CD

– Top-down treatment is disease-modifying
– Top-down treatment induces mucosal healing more frequently
– Top-down treatment induces long-term remission
– Step-up treatment has significant disadvantages

What Assumptions Are the Bases of the Discussion of 'Top Down' versus 'Step Up'?

What are the assumptions put forward to support a top-down approach in CD therapy? The most important assumptions made in favor of a top-down approach are depicted in table 1. It is stated that top-down treatment is disease-modifying, meaning that the 'natural course' of CD is changed. It may be argued that any therapy will change the 'natural course' of a disease, if 'natural' means the disease course without any intervention. It is obvious that some difficulties in the interpretation of the assumption that top-down treatment is disease-modifying is caused by the unclear meaning of 'natural' disease course. The term has been adopted from rheumatology. However, nonbiological therapy may also prevent joint destruction to some extent even in rheumatology. A further argument for a top-down approach is that top-down treatment induces mucosal healing more frequently. When compared to other drugs, this is certainly the case. Obviously, top-down treatment has the highest chance of inducing mucosal healing. However, we are still far from achieving mucosal healing in the majority of initially treated patients. Being 'better' still could mean that an attempt to achieve mucosal healing can be undertaken with other drugs, but in case of failure it may be switched to a biological. This is currently being investigated in the CALM trial, which is a very important clinical study. Achieving more often mucosal healing subsequently is not a very good argument for a top-down approach. The next argument for a top-down approach is that top-down treatment induces long-term remission. This, however, would only be a relevant argument if the same combination of drugs (i.e. biologicals and immunosuppressants) would not achieve long-term remission in a step-up ap-

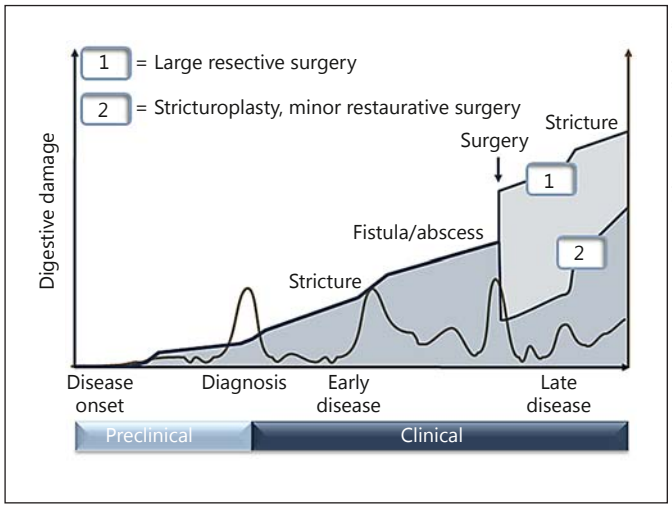

Fig. 1. Disease courses in CD. Clinical activity may not reflect ongoing intestinal damage. Inflammation may be subclinical and result in cumulative tissue damage. Surgery may add additional tissue damage and loss of function, or may restore function and reduce damage at least partially (modified according to [47]).

proach. A final argument for top down is that step-up treatment has significant disadvantages such as more days off work and more days of physical impairment and reduced quality of life.

Those arguments of course are to some extent interrelated and not completely separate or different. If the top-down treatment induces mucosal healing more frequently, then it will likely be associated with better remission rates and better long-term remission. A CD patient in long-term remission will experience less intestinal damage. Therefore, this would indeed be of great influence on the disease course.

Pariente et al. [47] summarized this concept in an intriguing graph (fig. 1). If we only monitor the clinical activity of CD (as it is still recommended in many guidelines), there may be subclinical disease activity causing damage to the intestinal mucosa or the intestinal wall. In the original figure by Pariente et al., surgery always caused more damage to the gut indicating that it should be avoided under any circumstances. Clinical reality argues against that. Only major resective surgery will cause additional damage to the intestine. Stricturoplasty or small resective surgery, fistula surgery, or abscess drainage will improve intestinal function and reduce the 'digestive damage'. We need to be fair with our surgical colleagues at that point. Therefore, it is necessary to modify this scheme to better reflect clinical reality (fig. 1).

What Evidence Do We Have to Support a 'Top-Down' Approach?

There are some good arguments for early use of immunosuppressants or biologicals in a subgroup of CD patients. Most of the arguments, however, are of an indirect nature.

Indirect Evidence

With respect to clinical remission, subjects randomized to adalimumab in CHARM who enrolled in ADHERE were analyzed in an intention-to-treat approach with respect to treatment efficacy in relation to disease duration [48]. The analysis was strict as subjects who moved to open-label therapy in CHARM were classified as nonremitters from that point forward [48]. Subjects who moved to every-week therapy during ADHERE were also classified as nonremitters from that point forward. Furthermore, missing data were classified as nonremission. With those strict criteria, 55% of the patients with a CD duration of less than 2 years achieved a remission 58 weeks after CHARM baseline, whereas only 40% or less of patients that suffered from CD for 2–5 years or more than 5 years were in remission (CDAI <150) [48]. This difference was still obvious 164 weeks after the CHARM baseline, but less pronounced [48].

Besides clinical remission rates, mucosal healing has been analyzed in detail. In the SONIC trial, early anti-TNF-based therapy was associated with sustained steroid-free remission and complete mucosal healing [41]. In SONIC, AZA was compared to infliximab and the combination of both, a situation that cannot be directly compared to a top-down versus step-up situation.

In the above-mentioned top-down versus step-up study by D'Haens and colleagues [49], clinical remission rates were similar at week 104, but mucosal healing rate was higher with early anti-TNF therapy as compared to step-up therapy. In those patients, mucosal healing was a strong predictor of steroid-free remission [49]. In the STORI study performed by the GETAID, mucosal healing predicted maintenance of clinical remission when anti-TNF therapy was discontinued [45]. In the EXTEND trial, early anti-TNF use was associated with a higher rate of mucosal healing than later use [50]. This is in line with earlier reports indicating that anti-TNF antibodies induce mucosal healing more effectively in comparison to steroid therapy or immunosuppression [51–53]. Patients achieving mucosal healing have better long-term disease courses in population-based cohorts as seen in the IBSEN study [6].

Direct Evidence

One of the first trials investigating early treatment of IBD was the trial by Markowitz et al. [54] in pediatric patients who received 6-MP right after the diagnosis of IBD. In a prospective placebo-controlled multicenter trial, the combination of 6-MP (or placebo) and prednisone as therapy for 55 children with newly diagnosed moderate-to-severe CD was evaluated. In the 6-MP group, the duration of steroid use was significantly shorter and the cumulative steroid dose was significantly lower. Remission was induced in 89% of both groups, but only 9% of the 6-MP group relapsed compared with 47% of the placebo controls. Markowitz and colleagues concluded that early immunosuppression with '6-MP should be part of the *initial* treatment regimen for children with newly diagnosed moderate-to-severe CD', which reflects a top-down approach.

The most important argument for a top-down treatment is the clinical trial published by D'Haens et al. [46] in *The Lancet*. They assessed the success rates of a top-down versus a step-up therapy in 'newly diagnosed' CD of less than 4 years' duration (n = 129) [46]. The patients had to be naïve to immunomodulators and biologicals. The top-down group (n = 65) received AZA and infliximab in weeks 0, 2 and 5 and then later the anti-TNF in an 'on-demand' strategy. The step-up group (n = 64) received steroids as a first-line therapy, AZA or MTX in a second step and infliximab as a third-line therapy. The coprimary endpoints (CDAI <150 *and* no steroids *and* no surgery) were significantly different for both groups at weeks 24 and 52; however, there was no difference at week 80 and 104 [46, 49]. At the end of the observation period, the relative amount of patients receiving infliximab did not significantly differ and was around 20% [46, 49]. However, by definition the amount of patients receiving immunosuppressants was up to 100% in the top-down group, whereas it was around 80% in the step-up group, which indicates that in 20% of patients steroids induced a long-lasting remission without further need of escalation of therapy [46, 49].

Mucosal healing was significantly more frequent in the top-down group in 71% of patients, whereas it was only achieved in 30% of the step-up patients.

Weighing the Value of Top-Down Therapy

The benefits of a top-down approach according to the above-mentioned data are rather clear. There seems to be a better maintenance of remission after achieving it.

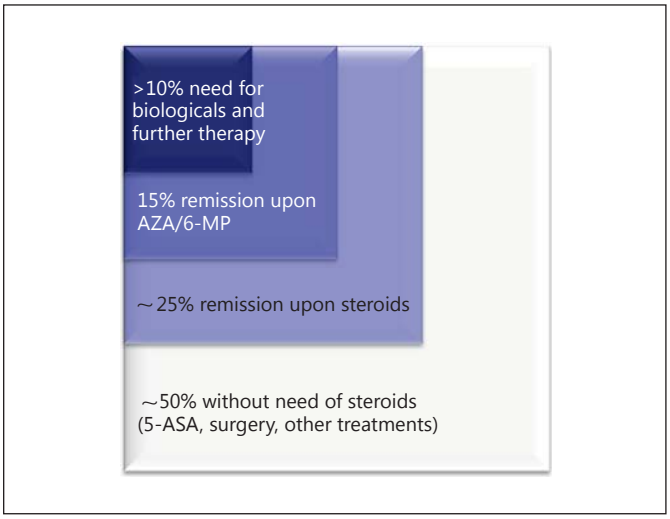

Fig. 2. Need for therapies among CD patients in population-based cohorts.

Bowel function is more rapidly improved, which is associated with an earlier improvement of the quality of life. The earlier promotion of mucosal healing may prevent complications such as perforations and obstructions [55–57].

On the other hand, there are also significant disadvantages of a top-down approach if applied to all patients without selecting those at risk for a complicated disease course. There are significant side effects of a more aggressive therapy to consider. The costs raised by a top-down approach for every CD patient would be significant and no health care system could cover such a strategy, making it unrealistic in the end. The majority of patients may not require more potent treatment, at least initially.

With this in mind we also should consider the data from the Norwegian population-based IBSEN study [6]. The investigators identified four primary courses of CD and asked 197 patients to identify which curve best matched their disease course over the 10 years since diagnosis [6]. As these four distinct disease courses suggest, no single management plan will suit all patients. CD management must therefore be tailored to the individual patient.

The IBSEN study data suggest that 43% of patients may have a mild disease course and not require intensive therapy [6] (fig. 2). However, the majority of patients is likely to have chronic disease and may benefit from early intensive management.

Would an 'Accelerated Step-Up Treatment' Cause a Disadvantage and Damage to IBD Patients?

A very important question with respect to a decision between the top-down or step-up approach is whether a step-up approach would indeed mean a significant disadvantage for the patient as mentioned above. Cosnes et al. [58] compared accelerated step-up care with early or immediate start of immunosuppressants (early AZA, n = 66) with conventional step-up therapy (n = 68) in patients with CD. The randomized open-label controlled trial was conducted in 24 centers between 2005 and 2010. The aim of this study was to compare the accelerated step-care strategy in patients with early CD and predictors of disabling disease (age at diagnosis <40, steroid use at first flare, perianal disease) with conventional therapy using steroids for the flare. Interestingly (in contrast to the Markowitz study in children), early AZA use in patients at high risk for disabling disease had no significant impact on the subsequent 3-year CD course [58]. Sixty-two percent of those CD patients assigned to the on-demand AZA group required AZA after a median follow-up of 5.6 months. No significant differences were found between the two groups with respect to time spent in remission. Among the patients receiving early AZA ('top down'), 29% required additional treatment with anti-TNF agents, similar to 26% in the steroid first/on-demand group who needed additional anti-TNF treatment. There was a trend to higher rates of unplanned perianal surgery in the steroid-treated patients. A similar trend was observed for intestinal surgery: 11% of those who received early AZA and 21% of patients who started with steroids in the 'classical step-up' approach required intestinal surgery without statistical significance between the groups (which could indicate that the study was not sufficiently powered). CDAI and CRP scores were not different between the groups [58].

The authors mention that conventional therapy could allow the patient to be vaccinated before immunomodulator therapy [58]. Overall, the step-up approach (which still was an 'accelerated' approach applying immunosuppressant after a first failed steroid course) had no significant disadvantage in this setting. It is important to note that the authors tried to select patients with early disease and high risk for complicated disease course. Nevertheless, at the end of the study more than one third of the patients in the step-up group had not met the criteria for requiring AZA [58].

Indirect evidence also comes from another study. Sorrentino et al. [59] investigated whether infliximab, not given immediately after surgery to prevent recurrence of CD but immediately after detection of postoperative endoscopic recurrence, could induce endoscopic remission at 54 weeks. Forty-three patients with ileocolonic CD and ileocecal resection were included and underwent colonoscopy 6 months after surgery. Twenty-four out of 43 patients had an endoscopic recurrence at 6 months. Thirteen were treated with infliximab, out of which 54% achieved endoscopic remission at 54 weeks and none had clinical recurrence. Again this study may be underpowered to detect a disadvantage of the delayed therapy and the observation period may be too short. In the study reported by Regueiro et al. [60], the rate of endoscopic recurrence at 1 year was only 9% (1 of 11 patients). This could indeed indicate a benefit from a 'top-down' approach in this situation. However, at the moment we do not have clear evidence indicating that 'accelerated step-up' upon demand is of disadvantage even for patients at some risk for complicated disease course.

Summary

A significant number of patients would be overtreated if a top-down therapy approach would be recommend for all patients diagnosed with CD (fig. 2). This would put patients with a mild and uncomplicated disease course at an unnecessary risk for therapy side effects and complications. Furthermore, there is no scientific evidence that an 'accelerated step-up' treatment (within the first or the first 2 years of disease) is of any disadvantage for the CD patient that develops a more severe disease. Most post hoc analyses in the respective anti-TNF trials indicating a better treatment effect in 'early' disease usually looked at a group that had the disease for 2 years or less [61].

In an area in which – with good reasons – we favor an individualized therapy as well as personalized medicine, a top-down approach for all CD patients is displaced. A 'one-size-fits-all' therapy principle only reflects a nonpersonalized and nonindividualized therapy approach. Either we are able to detect better predictors of CD disease course or we only apply a top-down therapy to the patient group at high risk for complications. A step-wise (but nevertheless rapid) therapy escalation can take individual patient preferences and needs into account. A timely progression from ineffective therapy to the next step of treatment is mandatory to avoid disadvantages. This needs to be based on up-to-date knowledge and clinical trials. Subsequently, careful patient selection will certainly justify the top-down approach in a subgroup of CD patients. However, the selection criteria need to be further investigated and improved.

Acknowledgements

This work was supported by a grant from the Swiss National Science Foundation: 3347CO-108792 (Swiss IBD Cohort).

Disclosure Statement

G.R. has consulted to Abbott Switzerland and Abbott International, Tillots International, to FALK Germany, to Essex/MSD Switzerland, Novartis, Roche, and Vifor Switzerland; has received speaker's honoraria from Abbott, FALK, MSD, Phadia, Tillots, UCB, and Vifor; and has received educational grants and research grants from Abbott, Ardeypharm, Essex/MSD, FALK, Flamentera, Novartis, Tillots, UCB and Zeller.

References

1 Dignass A, Van Assche G, Lindsay JO, Lemann M, Soderholm J, Colombel JF, Danese S, D'Hoore A, Gassull M, Gomollon F, Hommes DW, Michetti P, O'Morain C, Oresland T, Windsor A, Stange EF, Travis SP: The second European evidence-based consensus on the diagnosis and management of Crohn's disease: current management. J Crohns Colitis 2010;4:28–62.
2 Gordon M, Naidoo K, Thomas AG, Akobeng AK: Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. Cochrane Database Syst Rev 2011;1:CD008414.
3 Akobeng AK, Gardener E: Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. Cochrane Database Syst Rev 2005;1:CD003715.
4 Hanauer SB, Stromberg U: Oral pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. Clin Gastroenterol Hepatol 2004;2:379–388.
5 Dignass A, Marteau P: Mesalamine in the treatment of active Crohn's disease. Gastroenterology 2005;128:245–246.
6 Solberg IC, Vatn MH, Hoie O, Stray N, Sauar J, Jahnsen J, Moum B, Lygren I: Clinical course in Crohn's disease: results of a Norwegian population-based ten-year follow-up study. Clin Gastroenterol Hepatol 2007;5:1430–1438.
7 Henriksen M, Jahnsen J, Lygren I, Aadland E, Schulz T, Vatn MH, Moum B: Clinical course in Crohn's disease: results of a five-year population-based follow-up study (the IBSEN study). Scand J Gastroenterol 2007;42:602–610.
8 Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH: Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2008;3:CD000296.
9 Greenberg GR, Feagan BG, Martin F, Sutherland LR, Thomson AB, Williams CN, Nilsson LG, Persson T: Oral budesonide for active Crohn's disease. Canadian Inflammatory Bowel Disease Study Group. New Engl J Med 1994;331:836–841.
10 Rutgeerts P, Lofberg R, Malchow H, Lamers C, Olaison G, Jewell D, Danielsson A, Goebell H, Thomsen OO, Lorenz-Meyer H, et al: A comparison of budesonide with prednisolone for active Crohn's disease. New Engl J Med 1994;331:842–845.
11 Campieri M, Ferguson A, Doe W, Persson T, Nilsson LG: Oral budesonide is as effective as oral prednisolone in active Crohn's disease. The Global Budesonide Study Group. Gut 1997;41:209–214.
12 Mantzaris GJ, Christidou A, Sfakianakis M, Roussos A, Koilakou S, Petraki K, Polyzou P: Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. Inflamm Bowel Dis 2009;15:375–382.
13 Bar-Meir S, Chowers Y, Lavy A, Abramovitch D, Sternberg A, Leichtmann G, Reshef R, Odes S, Moshkovitz M, Bruck R, Eliakim R, Maoz E, Mittmann U: Budesonide versus prednisone in the treatment of active Crohn's disease. The Israeli Budesonide Study Group. Gastroenterology 1998;115:835–840.
14 Caesar I, Gross V, Roth M, Andus T, Schmidt C, Raedsch R, Weber A, Gierend M, Ewe K, Scholmerich J: Treatment of active and post-active ileal and colonic Crohn's disease with oral pH-modified-release budesonide. German budesonide study group. Hepatogastroenterology 1997;44:445–451.
15 Almawi WY, Beyhum HN, Rahme AA, Rieder MJ: Regulation of cytokine and cytokine receptor expression by glucocorticoids. J Leukocyte Biol 1996;60:563–572.
16 Herfarth H, Gross V, Andus T, Caesar I, Vogelsang H, Adler G, Malchow H, Petri A, Gierend M, Scholmerich J: Analysis of the therapeutic efficacy of different doses of budesonide in patients with active Crohn's ileocolitis depending on disease activity and localization. Intern J Colorectal Dis 2004;19:147–152.
17 Modigliani R, Mary JY, Simon JF, Cortot A, Soule JC, Gendre JP, Rene E: Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'etude therapeutique des affections inflammatoires digestives. Gastroenterology 1990;98:811–818.
18 Benchimol EI, Seow CH, Steinhart AH, Griffiths AM: Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2008;2:CD006792.
19 Pearson DC, May GR, Fick G, Sutherland LR: Azathioprine for maintaining remission of Crohn's disease. Cochrane Database Syst Rev 2000;2:CD000067.
20 Fraser AG: Methotrexate: first-line or second-line immunomodulator? Eur J Gastroenterol Hepatol 2003;15:225–231.
21 Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, DeWoody KL, Schaible TF, Rutgeerts PJ: A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. New Engl J Med 1997;337:1029–1035.
22 Hanauer SB, Sandborn WJ, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh D, Panaccione R, Wolf D, Pollack P: Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323–333.
23 Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, Schreiber S: Certolizumab pegol for the treatment of Crohn's disease. New Engl J Med 2007;357:228–238.
24 Sandborn WJ, Hanauer SB, Rutgeerts P, Fedorak RN, Lukas M, MacIntosh DG, Panaccione R, Wolf D, Kent JD, Bittle B, Li J, Pollack PF: Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. Gut 2007;56:1232–1239.
25 Schreiber S, Rutgeerts P, Fedorak RN, Khaliq-Kareemi M, Kamm MA, Boivin M, Bernstein CN, Staun M, Thomsen OO, Innes A: A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. Gastroenterology 2005;129:807–818.
26 Hanauer SB, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Rutgeerts P: Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–1549.
27 Colombel JF, Sandborn WJ, Rutgeerts P, Enns R, Hanauer SB, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent JD, Pollack PF: Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52–65.

28 Sandborn WJ: Clinical perspectives in Crohn's disease. Moving forward with anti-TNF-alpha therapy: current needs and future treatments. Rev Gastroenterol Disord 2007; 7(suppl 2):S23–S35.
29 Schreiber S, Khaliq-Kareemi M, Lawrance IC, Thomsen OO, Hanauer SB, McColm J, Bloomfield R, Sandborn WJ: Maintenance therapy with certolizumab pegol for Crohn's disease. New Engl J Med 2007;357:239–250.
30 Molnar T, Farkas K, Nyari T, Szepes Z, Nagy F, Wittmann T: Frequency and predictors of loss of response to infliximab or adalimumab in Crohn's disease after one-year treatment period – a single center experience. J Gastrointestin Liver Dis 2012;21:265–269.
31 Yanai H, Hanauer SB: Assessing response and loss of response to biological therapies in IBD. Am J Gastroenterol 2011;106:685–698.
32 Billioud V, Sandborn WJ, Peyrin-Biroulet L: Loss of response and need for adalimumab dose intensification in Crohn's disease: a systematic review. Am J Gastroenterol 2011;106: 674–684.
33 Ben-Horin S, Chowers Y: Review article: loss of response to anti-TNF treatments in Crohn's disease. Aliment Pharmacol Ther 2011;33:987–995.
34 Chao J, Mulani P: What is the rate of loss of response to infliximab therapy in Crohn's disease? Am J Gastroenterol 2009;104:2353–2354.
35 Gisbert JP, Panes J: Loss of response and requirement of infliximab dose intensification in Crohn's disease: a review. Am J Gastroenterol 2009;104:760–767.
36 Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P: Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106:644–659.
37 Faubion WA Jr, Loftus EV Jr, Harmsen WS, Zinsmeister AR, Sandborn WJ: The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology 2001;121:255–260.
38 Sandborn W, Sutherland L, Pearson D, May G, Modigliani R, Prantera C: Azathioprine or 6-mercaptopurine for inducing remission of Crohn's disease. Cochrane Database Syst Rev 2000;2:CD000545.
39 Sandborn WJ, Feagan BG, Lichtenstein GR: Medical management of mild to moderate Crohn's disease: evidence-based treatment algorithms for induction and maintenance of remission. Aliment Pharmacol Ther 2007;26: 987–1003.
40 Kirwan JR: Conceptual issues in scoring radiographic progression in rheumatoid arthritis. J Rheumatol 1999;26:720–725.
41 Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, Lichtiger S, D'Haens G, Diamond RH, Broussard DL, Tang KL, van der Woude CJ, Rutgeerts P: Infliximab, azathioprine, or combination therapy for Crohn's disease. New Engl J Med 2010;362:1383–1395.
42 Schnitzler F, Fidder H, Ferrante M, Noman M, Arijs I, Van Assche G, Hoffman I, Van Steen K, Vermeire S, Rutgeerts P: Long-term outcome of treatment with infliximab in 614 patients with Crohn's disease: results from a single-centre cohort. Gut 2009;58:492–500.
43 Louis E, Belaiche J, Reenaers C: Anti-tumor necrosis factor nonresponders in Crohn's disease: therapeutic strategies. Dig Dis 2009;27: 351–357.
44 Allez M, Vermeire S, Mozziconacci N, Michetti P, Laharie D, Louis E, Bigard MA, Hebuterne X, Treton X, Kohn A, Marteau P, Cortot A, Nichita C, van Assche G, Rutgeerts P, Lemann M, Colombel JF: The efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF antibodies. Aliment Pharmacol Ther 2010;31:92–101.
45 Louis E, Mary JY, Vernier-Massouille G, Grimaud JC, Bouhnik Y, Laharie D, Dupas JL, Pillant H, Picon L, Veyrac M, Flamant M, Savoye G, Jian R, Devos M, Porcher R, Paintaud G, Piver E, Colombel JF, Lemann M: Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. Gastroenterology 2012;142:63–70.
46 D'Haens G, Baert F, van Assche G, Caenepeel P, Vergauwe P, Tuynman H, De Vos M, van Deventer S, Stitt L, Donner A, Vermeire S, Van de Mierop FJ, Coche JC, van der Woude J, Ochsenkuhn T, van Bodegraven AA, Van Hootegem PP, Lambrecht GL, Mana F, Rutgeerts P, Feagan BG, Hommes D: Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet 2008;371:660–667.
47 Pariente B, Cosnes J, Danese S, Sandborn WJ, Lewin M, Fletcher JG, Chowers Y, D'Haens G, Feagan BG, Hibi T, Hommes DW, Irvine EJ, Kamm MA, Loftus EV Jr, Louis E, Michetti P, Munkholm P, Oresland T, Panes J, Peyrin-Biroulet L, Reinisch W, Sands BE, Schoelmerich J, Schreiber S, Tilg H, Travis S, van Assche G, Vecchi M, Mary JY, Colombel JF, Lemann M: Development of the Crohn's disease digestive damage score, the Lemann score. Inflam Bowel Dis 2011;17:1415–1422.
48 Schreiber S, Reinisch W, Colombel JF, Sandborn WJ, Hommes DW, Robinson AM, Huang B, Lomax KG, Pollack PF: Subgroup analysis of the placebo-controlled charm trial: Increased remission rates through 3 years for adalimumab-treated patients with early Crohn's disease. J Crohns Colitis 2013;7:213–221.
49 Baert F, Moortgat L, Van Assche G, Caenepeel P, Vergauwe P, De Vos M, Stokkers P, Hommes D, Rutgeerts P, Vermeire S, D'Haens G: Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology 2010;138:463–468.
50 Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, Reinisch W, Kumar A, Lazar A, Camez A, Lomax KG, Pollack PF, D'Haens G: Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the extend trial. Gastroenterology 2012;142:1102–1111.
51 Rutgeerts P, Diamond RH, Bala M, Olson A, Lichtenstein GR, Bao W, Patel K, Wolf DC, Safdi M, Colombel JF, Lashner B, Hanauer SB: Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endoscopy 2006;63:433–442.
52 Rutgeerts P, Feagan BG, Lichtenstein GR, Mayer LF, Schreiber S, Colombel JF, Rachmilewitz D, Wolf DC, Olson A, Bao W, Hanauer SB: Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004;126: 402–413.
53 Sandborn WJ: Mucosal healing in inflammatory bowel disease. Rev Gastroenterol Dis 2008;8:271–272.
54 Markowitz J, Grancher K, Kohn N, Lesser M, Daum F: A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenterology 2000;119:895–902.
55 Lichtenstein GR, Cuffari C, Kane SV, Hanauer S, Present DH: Maintaining remissions across the lifespan: a roundtable discussion with Crohn's disease experts. Inflamm Bowel Dis 2004;10(suppl 2):S11–S21.
56 Lichtenstein GR, Hanauer SB, Kane SV, Present DH: Crohn's is not a 6-week disease: lifelong management of mild to moderate Crohn's disease. Inflamm Bowel Dis 2004; 10(suppl 2):S2–S10.
57 Caprilli R, Angelucci E, Cocco A: Early or late guided missile in the treatment of Crohn's disease? Dig Liver Dis 2005;37:973–979.
58 Cosnes J, Bourrier A, Bouhnik Y, Laharie D, Nahon S, Bonnet J, Carbonnel F, Dupas J, Jean Marie R, Jouet P, Savoye G, Mary J, Colombel JF: Accelerated step-care therapy with early azathioprine (AZA) vs. conventional step-care therapy in Crohn's disease. A randomized study. Gastroenterology 2012;142 (suppl 1):161.
59 Sorrentino D, Terrosu G, Paviotti A, Geraci M, Avellini C, Zoli G, Fries W, Danese S, Occhipinti P, Croatto T, Zarifi D: Early diagnosis and treatment of postoperative endoscopic recurrence of Crohn's disease: partial benefit by infliximab – a pilot study. Dig Dis Sci 2012; 57:1341–1348.
60 Regueiro M, Schraut W, Baidoo L, Kip KE, Sepulveda AR, Pesci M, Harrison J, Plevy SE: Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009;136:441–450.
61 Fasci Spurio F, Aratari A, Margagnoni G, Doddato MT, Papi C: Early treatment in Crohn's disease: do we have enough evidence to reverse the therapeutic pyramid? J Gastrointestin Liver Dis 2012;21:67–73.