REVIEWS

Early Treatment in Crohn's Disease: Do We Have Enough Evidence to Reverse the Therapeutic Pyramid?

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Abstract

Current guidelines on the medical therapy of Crohn's disease recommend a step-up strategy consisting of a progressive intensification of treatment as the disease severity increases. In the last fifteen years, the introduction of biologic therapies, particularly anti-TNFα antibodies, has offered new therapeutic opportunities. The efficacy of anti-TNFα therapy for inducing and maintaining clinical response or remission in moderate to severe Crohn's disease has been extensively evaluated in randomised controlled trials and meta-analyses. Moreover, anti-TNFα therapy can induce mucosal healing and this property may be potentially disease-modifying. Consequently, an early introduction of biologics and/or immunomodulators (top-down strategy) in newly diagnosed Crohn's disease has been advocated. This paper will review the evidence in favour and against this approach to Crohn's disease therapy, discuss which patients are potential candidates to early aggressive treatment, and how a conventional step-up approach can be optimized. The conclusion is that an indiscriminate top-down approach does not seem to be appropriate for all patients with moderate to severe Crohn's disease.

Key words

Biologic therapy – infliximab – adalimumab – immunosuppressive agents – azathioprine – Crohn's disease.

Introduction

Crohn's disease (CD) is a chronic inflammatory disease of unknown aetiology that may affect any part of the gastrointestinal tract. The disease has a chronic relapsing course and may be treated with medical and surgical procedures but is not cured. Population-based studies have shown that the clinical course is favourable for the majority patients and only approximately 50% will need systemic corticosteroids during the course of the disease [1-3]. However, a subgroup of patients show an evolutive and disabling course towards stricturing and penetrating complications; surgical resection, and eventually repeated operations may occur [4-7]. Moreover, long-standing disease is associated with an increased risk of colorectal and small bowel cancer [8], and overall mortality may be slightly higher than expected [9]. Predicting the clinical course could be important in order to tailor management for each patient.

The traditional therapeutic approach of CD is based on the so-called step-up strategy, consisting of progressive intensification of treatment as the disease severity increases. Less toxic drugs, but often less efficacious, are used in mild disease, whereas more efficacious drugs, but potentially more toxic, are employed in severe disease or in patients unresponsive to first-line therapy. This strategy is recommended by current guidelines [10] and is aimed at therapeutic end points such as induction and maintenance of clinical remission, steroids withdrawal and prevention of post-operative recurrence. However, the natural course of the disease, in terms of reduction of complications and the need for surgery, seems to have not been modified by conventional treatment [11].

In the last 15 years, the advent of biologic therapies, particularly anti-TNFα antibodies (infliximab, adalimumab, certolizumab), has offered new options in the management of CD. Several randomised controlled trials (RCTs) and meta-analyses have shown the efficacy of anti-TNFα therapy for inducing and maintaining clinical response and remission in moderate to severe CD [12-23]. Seemingly, anti-TNFα therapy can also induce rapid and sustained mucosal healing, and may contribute to fistula closure or to reduction in fistula drainage: these properties may offer the potentiality to modify the course of CD, possibly by reducing complication rates, the need for hospitalization and surgical resections

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[24-26]. To date, the vast majority of patients enrolled in RCTs addressing anti-TNFα antibodies had advanced disease in terms of duration (length of more than 7 years) and refractoriness to conventional therapies: approximately 30%-50% of patients had active disease despite receiving steroids and/or immunomodulators at the time of randomization. At present, biologic therapies are usually employed in clinical practice for patients with moderate to severe disease who fail to respond to conventional medical treatment, but new questions are currently facing gastroenterologists: at what point in the natural history of CD should anti-TNFα agents be used? Should an earlier use be encouraged? What can be expected from an early treatment: just a higher probability of clinical response and remission or a real change in the disease course? Is the proposed reversal of the traditional so called therapeutic pyramid (top-down approach) really supported by strong evidence? In this paper we will try to give answers to these questions.

Is an early use of anti-TNFa agents more effective for achieving clinical response or remission?

Uncontrolled data in paediatric patients suggested that infliximab treatment has been associated with a higher response rate in patients with short disease duration compared to those with a long history of disease [27, 28]. The REACH study [29] on moderate-severe paediatric CD patients treated with scheduled infliximab, showed that the percentage of patients achieving clinical response was 73.1% and 63.5% at 30 and 54 weeks respectively, and the percentage of those achieving clinical remission was 59.6% and 53.8% at 30 and 54 weeks, respectively. These figures represent an approximate 20% increase in response and remission rates compared with the adult population of the ACCENT I study [15]. It can be speculated that this difference may be due to the shorter disease duration in the paediatric population enrolled in the REACH study (mean 2.0 ± 1.4 years), compared to the adult population enrolled in the ACCENT I study (median 7.9 years, range 3.9 - 14.7).

Similarly, subgroup analysis of the CHARM study (adalimumab) [30] and data of the PRECISE 2 study (certolizumab) [31] suggest that response and remission rates can be affected by disease duration. In the CHARM study, patients with a disease duration of less than 2 years had an approximately 20% increase in remission rates at 26 and 56 weeks compared to patients with a disease duration greater than 5 years [30]. In the PRECISE 2 study CD patients treated with certolizumab earlier rather than later, achieved better treatment outcomes [31].

In the study of D'Haens et al [32], 133 patients with moderate-severe CD with disease duration of less than 4 years and corticosteroids/immunomodulators naïve, were randomized to early treatment with infliximab and azathioprine (AZA) (top-down approach) or conventional management (step-up approach). The percentage of patients in clinical remission and off steroids or surgery at 6 and 12 months was significantly higher in the top-down group. Moreover, at 2 years, mucosal healing occurred more frequently in the top-down group and complete mucosal healing was associated with a significantly higher steroid-free remission rates in the subsequent 2 years [33].

Taken together, these data seem to suggest the presence of a particular period in which biological therapies could be more efficacious in terms of clinical response and remission but do not provide strong evidence. Indeed, comparing the REACH and ACCENT I studies is not methodologically correct if disease duration is considered the only variable potentially associated with a higher probability of response. As a matter of fact, not only the patients' populations of the two studies are not comparable (paediatric patients in the REACH study and adult patients in the ACCENT I study) but also in the REACH study more than 90% of patients were receiving concomitant immunomodulators at the time of randomization, compared to only 30% in the ACCENT I study. The subgroup analysis in the CHARM and PRECISE studies [30, 31] is a post-hoc analysis and can generate a hypothesis but does not provide strong evidence. Finally, the study of D'Haens et al [32] is susceptible to several methodological criticisms. Firstly, it is an open label study; secondly, the step-up treatment is suboptimal considering the dose of corticosteroids (40 mg/day) and the use of budesonide in moderate to severe disease; lastly, in the conventional treatment group no maintenance therapy is offered and late immunosuppressive treatment is reserved only for steroid-dependent patients.

In conclusion, although an early use of anti-TNFα agents may be attractive, no strong evidence supports that this approach is more effective than an optimised conventional strategy in terms of the probability of long term clinical response or remission.

Can the early use of anti-TNFα agents modify the natural course of disease?

Early treatment is based on the hypothesis that the long-term disease course could be modified. Considering that CD has a lifelong, potentially evolutive and disabling course, only clinically relevant and long term end points could measure changes in the disease course; these include occurrence of complications, need for surgical resection or re-operations, risk of cancer and mortality. Nowadays, studies considering and measuring these end points are lacking and the hypothesis that early treatment is disease modifying is based on the evaluation of surrogate end points such as mucosal healing and reduction of hospitalizations and surgery. Two aspects should be considered: are these end points valid surrogates? Is the duration of follow-up long enough to demonstrate a reduction of incidence of unpredictable events, such as development of complications or need of surgery?

Data addressing mucosal healing are available from different sources: subgroup analysis of RCTs designed for evaluating different end-points, observational cohort studies,

and, more recently, RCTs including mucosal healing as primary or secondary end-point.

In the ACCENT I study, 99 patients out of 573 randomised, underwent an endoscopic substudy [24]. Scheduled infliximab every 8 weeks permitted mucosal healing in approximately 50% of patients at 54 weeks, and sustained mucosal healing (at week 10 and week 54) in approximately 20-30% of patients; episodic treatment seemed to have, conversely, little impact on mucosal lesions [24]. In the study of D'Haens et al [32], a subset of 49 patients from the initially randomized cohort of 133 patients underwent colonoscopy at baseline and after 2 years of therapy. Ulcers regression at 104 weeks occurred in 19/26 (73.1%) patients receiving combined immunosuppression and in 7/23 (30.4%) patients receiving conventional step-up approach (p=0.002). In the experience of the University of Leuven, Belgium, in a cohort of 214 CD patients treated with infliximab, complete or partial mucosal healing was observed in 45.4% and 22.4% of patients, respectively after a median of 6.7 months after the start of infliximab [34]. Complete mucosal healing was defined as absence of ulcerations at follow up endoscopy in patients who had ulcerations at baseline, and partial mucosal healing was defined as clear endoscopic improvement but still with ulceration.

Recently, in the SONIC study [35], 508 adult patients with moderate to severe CD, immunomodulators and biologic naïve, were randomised to receive infliximab (5 mg/kg at weeks 0, 2 and 6, and then every 8 weeks), AZA 2.5 mg/kg, or a combination therapy with the two drugs for 30 weeks, with the possibility to continue in a blinded study extension up to 50 weeks. The primary efficacy end point was corticosteroid-free clinical remission at week 26 and mucosal healing was a secondary end point. Combination therapy was significantly more effective than infliximab monotherapy and AZA monotherapy for inducing corticosteroids-free remission at week 26 (56.8%, 44.4% and 30.0%, respectively). Mucosal healing was assessed in a subset of 309 patients of the 508 randomised. Forty-four per cent of patients receiving combination therapy achieved mucosal healing at week 26 compared to 30% of patients receiving infliximab monotherapy (p=0.06), and 16% of patients receiving AZA monotherapy (p=0.001 vs combination therapy and p=0.02 vs infliximab monotherapy) [35]. Despite the relevant result that combination therapy is better than monotherapy with infliximab or AZA, this trial has several drawbacks. The most relevant point is that only 64% of patients had endoscopic lesions at baseline and it is difficult to explain how patients with clinically active CD can have normal mucosa at endoscopy [36]. Moreover, when the analysis is restricted to the subset of patients with evidence of mucosal lesions and systemic inflammation (CRP > 0.8 mg/dl) at baseline (n=204), no difference in steroid-free remission at week 26 is observed between combination therapy and infliximab monotherapy (68.8% and 56.9%, respectively) [35]. More data addressing efficacy and safety are needed before combination therapy becomes the first choice treatment in active moderate-to-severe CD [36].

The EXTEND trial is the first trial that considered mucosal healing as a primary end point in assessing the efficacy of adalimumab in moderate to severe active ileo-colonic CD [37]. In this trial, 129 patients were randomized to receive either an induction treatment with adalimumab (160 mg at week 0 and 80 mg at week 2), followed by scheduled maintenance therapy (40 mg every other week), or the same induction treatment followed by placebo. After 12 and 52 weeks, mucosal healing (defined as endoscopic absence of mucosal ulcerations) was observed in 27.4% and 24.2% of patients in the treatment arm compared to 13.1% and 0% of those receiving placebo ($p = 0.056$ and $p < 0.001$, respectively).

These data suggest that anti-TNFα agents have the potentiality to achieve therapeutic goals beyond the control of symptoms. However, is mucosal healing a valid surrogate end point? A correlation between endoscopic lesions and symptoms often exists: mucosal lesions precede symptoms, and predict the risk of clinical recurrence in operated disease; severe mucosal lesions are considered the first step towards the development of septic and penetrating complications that require surgery, and maintenance of mucosal healing could potentially reduce the cancer risk. The reduction of hospitalization and surgery reported in clinical trials and observational studies is commonly attributed to a sustained mucosal healing [24-26, 34, 38]. In the pre-biologic era, a Norwegian Population-Based Cohort study showed that mucosal healing one year after diagnosis is predictive of a better disease course in terms of reduced disease activity, decreased need of active treatments and surgery [39, 40]. Crohn's disease is, however, a transmural disease and mucosal healing could not reflect complete healing of the lesions. In penetrating CD treated with infliximab, for example, it has been shown that closure of external fistula orifices does not correspond to a real closure of fistulous tracts [41]. A group called "The International Program to develop New Indexes in Crohn's Disease" (IPNIC) is trying to develop a new instrument that can measure the cumulative bowel damage and therefore "intestinal healing". This instrument, called the Crohn's Disease Digestive Damage Score (the Lemann score), should take into account the damage location, severity, extent, progression, and reversibility, and could be used as a more reliable surrogate end point to assess the effect of various medical therapies [42].

Recent data indicate that early treatment with infliximab may modify the natural history of post-operative CD. An open-label study by Sorrentino et al showed that infliximab and oral methotrexate, administered as prophylactic therapy for preventing post-operative recurrence, were more effective than mesalazine [43]. These preliminary observations have been recently confirmed in a randomised, double blind placebo controlled trial [44] in which 24 patients who had undergone ileo-colonic resection for CD, were assigned to receive infliximab or placebo for one year. The rate of endoscopic recurrence was significantly lower in the infliximab group (9.1% vs 84.6%; p=0.0006). Despite the small sample size of this study, the results are very impressive and indicate for the first time that anti-TNFα antibodies may

prevent post-operative recurrence and, potentially, may alter the natural history of CD.

In conclusion, even if mucosal healing and reduction of hospitalizations and surgery are clinically relevant end points in an individual CD patient, they cannot yet be considered as strong evidence that biologic therapy can really change the disease course in the long term.

Early therapy in Crohn's disease: not only biologics

The introduction of biologics has changed the approach to CD treatment. The potentiality of anti-TNFα antibodies to modify the natural course of the disease is very attractive and proposals of an early treatment are growing. However, some other important inputs come from the top-down paradigm: the optimization of the traditional therapeutic approach in terms of early identification of steroid-dependency, early use of immunomodulators and re-evaluation of surgical timing.

Early use of immunomodulators

Systemic corticosteroids are the gold standard in the treatment of active CD, but their major limitations are the temporary benefit, the ineffectiveness in maintaining remission and the high toxicity [45]. Observational studies [2, 3, 46, 47] have re-considered corticosteroid efficacy in the treatment of CD. In fact, despite a high short-term remission rate (approximately 80%), less than 50% of CD patients receiving steroids are still in remission after one year without prolonged corticosteroid treatment or surgery. From this point of view, steroid-refractoriness and steroid-dependency are the rule rather than the exception. In fact, at least 60% of CD patients that have started corticosteroids are potential candidates for immunosuppressive treatment. In the last years, we have assisted to the increased employment of immunomodulators [11], and studies on paediatric populations have shown the potential benefit of an early immunosuppressive therapy. In the study of Markowitz et al [48], 55 children with recent onset of disease were treated with systemic corticosteroids combined with mercaptopurine (6-MP) or placebo. In the short term (1 month) the remission rate was the same in the 2 groups: nevertheless the probability of relapse at 6 and 18 months was significantly lower in 6-MP treated patients than in the placebo group: 4% vs 28% ($p<0.007$) at 6 months, and 9% vs 47% ($p<0.007$) at 18 months, respectively. Observational studies in the paediatric population have shown that early introduction of immunomodulators is associated with a more favourable clinical course in terms of need of corticosteroids, hospitalisations and surgical resections [49, 50]. A population-based study on a cohort of 341 CD patients from Cardiff, (diagnosed between 1986 and 2003) analysed the changes in medical treatment and surgical resection rates over time [51]. The patients were divided into three groups according to the years of diagnosis (Group A=1986-1991, Group B=1992-1997 and Group C=1998-2003). The Kaplan Meyer analysis indicated an increased and earlier immunomodulators use in the recent years, associated with a significant reduction in long-term steroid use and cumulative probability of intestinal surgery. In a multivariate Cox analysis, year of diagnosis, disease location, oral corticosteroids within 3 months of diagnosis and early thiopurine use (within the first year of diagnosis) appeared all to be independent factors affecting the likelihood of intestinal surgery.

Re-evaluation of surgical timing

In the era of biologics, avoiding surgery is considered by many the most relevant clinical end point and an indicator of change in the disease course. However, it is difficult to unquestionably agree with this concept considering that surgery itself has turned out to be the most efficacious treatment in maintaining a prolonged clinical remission [52]. It may also be noted that CD is a heterogeneous entity, and that surgery may have different impacts based on different disease location, extension, and possible consequences of surgical resection. In other words, every effort should be made to avoid surgery when a definitive ileostomy or an extensive ileal or colonic resection is implied, but surgery may be a valid option in respect to a prolonged medical therapy in localized ileal or ileo-cecal CD. In fact, approximately 50% of patients maintain clinical remission and 65-75% do not need re-operation within 10 years from the first ileo-cecal resection [53, 54]. The 3 year clinical course of a steroid-dependent ileo-cecal CD patient treated with immunomodulators (and surgery in case of not response) or early surgery without immunosuppressive therapy, has been simulated by a Markov's decisional model [55]. Considering the efficacy of these two different approaches, the adverse effects of immunomodulators, the risk of complications, post-surgical mortality, and surgical recurrence, the two options resulted in being similar in terms of benefit/risk ratio, and both seem to be valid alternatives in ileo-cecal CD. In a retrospective study on 207 patients with ileo-caecal CD submitted to surgical resection and with a mean follow-up after surgery of 147 months (12 – 534), we showed that early surgery (performed at the time of diagnosis or within 6 months after diagnosis) was associated with a significantly lower risk of clinical recurrence within 10 years compared to surgery performed late in the course of the disease (Hazard Ratio, HR = 0.57; 95%CI 0.35-0.92; $p=0.02$) [54]. Therefore, a "surgical top-down" approach may be a valid strategy in localized ileal or ileo-cecal disease patients with a low surgical risk.

Early therapy with biologics: the risk/benefit ratio

An indiscriminate top-down strategy cannot be proposed for all CD patients for several reasons, in particular in order to avoid risks of an aggressive therapy in patients that would have an indolent disease course. Toxicity of biologic therapy in the long term and high costs should also be considered. The key to solve the problem would consist of the early identification of the subgroup of patients that will develop an aggressive disease course and, therefore, may benefit from an early biologic and/or immunosuppressive treatment.

Nowadays, unfortunately, we do not have valid and accurate predictors of the CD course and the decision to start a top-down strategy or an aggressive step-up approach (early use of conventional immunomodulators) is largely empirical and not routinely recommended. Major guidelines, however, suggest that an early introduction of immunomodulators or anti-TNFa therapy may be considered in selected patients with features of aggressive disease such as extensive ileal disease, upper gastrointestinal localization, rectal localization or perianal disease, and severe extra intestinal manifestations [10, 56]. Controlled, prospective and methodologically well designed studies are necessary in order to define if this approach may really modify the natural course of CD.

When considering an early and aggressive treatment, the balance between efficacy and safety of this approach should be carefully considered. The major concerns for a widespread use of biologics and/or immunomodulators are the long term safety issues, particularly the risk of severe opportunistic infections and the potential increased risk of neoplasia. Fortunately, most of the adverse events related to biologics are mild and transient. The overall risk of infection may be increased by biologic therapies but the risk of severe infections does not seem to be increased in RCTs and observational studies [22, 57] although combined immunosuppression can increase the risk of opportunistic infections [58]. Recently, it has been shown that advanced age may be a risk factor for severe infection: patients older than 65 years receiving anti-TNFa therapy for IBD have a high rate of severe infections and mortality compared with younger patients receiving the same drug or patients of the same age who did not receive anti-TNFa [59].

The most fearful concern of patients and doctors with prolonged use of biologic agents is the potential cancer risk. The overall risk of malignancies appears not to be increased in patients treated with anti-TNFa agents. This is supported by RCTs, meta-analyses, cohort studies, case control studies and post-marketing surveillance reports [22, 57, 60-62]. A particular concern was raised of a possible association between anti-TNFa agents and an increased risk of lymphoma, specifically non-Hodgkin's lymphoma. In a meta-analysis of 26 studies involving 8,905 patients and 21,178 patient years of follow up, it has been shown that, compared with the expected rate of non-Hodgkin's lymphoma, anti-TNFa teated subjects had approximately a 3 - fold increased risk of lymphoma although the absolute rate of these events is low [63]. However, the majority of patients developing lymphoma had previous immunomodulators' exposure and this raises the question whether the major contributors to the increased risk of lymphoma are the immunomodulators or anti-TNFa drugs considering that immunomodulators alone are associated with a 4-fold increased risk of lymphoma [64]. Hepatosplenic T-cell lymphoma, a rare and usually fatal lymphoma that primarily affects young men, has been associated with combined therapy with anti-TNFa and thiopurines, but no cases have been reported in IBD patients receiving only anti-TNFa therapy [65]. Major guidelines recommend avoiding combined maintenance treatment with anti-TNFa and thiopurines particularly in young patients [10, 56]. Another attempt to estimate the risk of lymphoma in patients treated with infliximab was recently addressed in a model looking specifically at lymphoma formation and mortality [66]. In the model comprising two cohorts of 100,000 patients each, an elevated risk of death (249 extra cases) and lymphoma (201 extra cases) was observed in patients receiving infliximab compared to patients receiving standard therapy. However, 12,216 more patients were in remission and 4,255 fewer surgeries were required to be performed in patients treated with infliximab.

In conclusion, biologics and immunomodulators offer such an important clinical benefit for patients with severe CD that withholding their use is not justifiable. The risk–benefit ratio of biologic therapy in IBD is therefore in favour of these agents provided that physicians administer these drugs with an awareness of their toxicity profile, select carefully patients who really require an aggressive approach, and examine them on a regular basis in order to prevent and treat any complication.

Conclusions

Over the last fifteen years, the development of anti-TNFα antibodies has offered new options in the management of CD. Although according to current guidelines, biologic agents should be used mainly for refractory disease (step-up approach), an earlier use of these agents has been often advocated. In fact, there is a growing body of data suggesting that the benefits of anti-TNFα therapy may extend beyond the sole control of symptoms. However, at the present time, there is insufficient evidence to universally adopt a top-down strategy into clinical practice. Preliminary data suggest that a more aggressive treatment can be justified in high-risk patients, both adults and children but, unfortunately, validated predictors of risk are still lacking. In properly selected patients, the benefits of biologics outweigh the risks. Perhaps the most important lesson from the top-down paradigm is the optimization of the traditional therapeutic approach in terms of limited steroid use, early identification of steroid-resistance and dependency, increased and earlier use of immunomodulators, and re-evaluation of surgical timing. As recently outlined in a prospective observational study, when treatment guidelines are strictly followed, high remission rates and low morbidity rates can be achieved within 5 years in newly diagnosed CD patients [62].

Conflicts of interest

None to declare.

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