INTRODUCTION

To date, medical therapy for Crohn's disease has been restricted to treat the signs and symptoms of the disease, to prevent steroid dependence by using immunomodulating agents (azathioprine, 6-mercaptopurine, methotrexate), to maintain clinical remission, and to minimize medication toxicity. The introduction of biologic therapy, particularly the use of anti-tumor necrosis factor alpha (TNFα) agents (infliximab, adalimumab, certolizumab pegol), has provided a powerful instrument in the treatment and management of Crohn's disease that has lead to an expansion of goals in Crohn's disease therapy. These include a rapidly achieved and sustained clinical remission, complete and sustained healing of the bowel mucosa, reduction in steroid use, reduction in hospitalizations and surgeries, avoidance of complications of the disease (stenoses, fistulas), and improvement of patients' overall quality of life. Infliximab, adalimumab, and certolizumab pegol have demonstrated efficacy for induction and maintenance of remission in Crohn's disease. However, biologic agents are still used with reluctance, being the high cost and the uncertainty about long-term safety of these agents the most frequently cited reasons. An important question facing physicians that take care of Crohn's disease patients is at what point of the disease should biological therapy be used.

STEP-UP APPROACH

The standard treatment in Crohn's disease is based on a step-up approach in which “traditional” therapies thought to be more secure are used early and then successive therapies are added in case of lack of response or toxicity. Under this scheme, agents with low efficacy such as aminosalicylates may be used for long periods of time without any benefit. Patients who fail to respond to aminosalicylates are then treated with prednisone or budesonide if the disease is limited...
to the ileum or the right colon. Corticosteroids are efficacious to induce remission in Crohn's disease patients but do not induce long-lasting remission[1]. About 40% of patients will develop a steroid-dependent or steroid-refractory course of the disease. In these cases, treatment with immunomodulating agents such as azathioprine, 6-mercaptopurine or methotrexate is started. Immunomodulation has long-term efficacy in inflammatory bowel disease but has limited value for induction of remission and benefits to less than half of the patients dependent or resistant to corticosteroids[2][4]. Under this therapeutic approach, population-based studies show that only 42% of Crohn's disease patients are symptom-free at 2 years after the initial diagnosis and 12% after 10 years, and that 10% of patients have chronically active disease in 2 years and 1% in 10 years[5]. Relapsing or chronically active disease leads to complications that often require surgical treatment that, unfortunately, does not cure or interrupt the progression of the disease[6]. Rates of surgical intervention remain high, with as many as one third of patients requiring surgery within a year of beginning oral corticosteroids[8] and with no significant decrease in the need of surgery in the last decades despite the earlier and increasing use of immunomodulators[9]. In the last years it has become also apparent that immunomodulators carry a significant safety risk for patients treated long term, including the risk of infection[9], lymphoma[11], cervical carcinoma[12], and nodular regenerative hyperplasia[13].

**TOP-DOWN APPROACH**

The ability of anti-TNFα agents to rapidly control disease symptoms and to heal the mucosa has raised the question of whether the early use of biological therapy in patients with newly diagnosed Crohn's disease can alter the course and natural history of the disease. In patients with early rheumatoid arthritis, initial combination therapy with high doses of prednisone and methotrexate or initial combination therapy with infliximab and methotrexate has shown to be more effective than sequential monotherapy or step-up combination therapy to prevent disease progression[14-18].

This concept, applied to Crohn's disease, has been tested in a trial carried out in Belgium, Holland and Germany by D'Haens et al[19]. This study included 133 patients with early Crohn's disease (defined as a diagnosis within the past 4 years) not previously treated with corticosteroids, immunomodulators or biological agents. Patients were randomly assigned to receive combined immunosuppression induction with azathioprine and three infusions of infliximab at weeks 0, 2, and 6 (n = 65) (top-down group), or to conventional therapy with two tapering courses of corticosteroids, and if indicated with azathioprine and then with infliximab (n = 64) (step-up group). Patients who were intolerant to azathioprine in both groups received methotrexate. Patients in the top-down group were given additional infliximab infusions in an “on-demand” basis and corticosteroids, if necessary, to control disease activity.

The primary outcome was the combination of remission without corticosteroids and without bowel resection at weeks 26 and 52. At week 26, 39/65 (60%) of patients in the top-down group were in clinical remission without corticosteroids and without surgery compared to 23/64 (36%) in the step-up group (P = 0.0062) with an absolute difference of 24% (95% CI 7.3-40.8). At week 52, 40/65 (61.5%) in the top-down group were in remission compared to 27/64 (42.2%) in the step-up group (P = 0.0278), with an absolute difference of 19.4% (95% CI 2.4-36.3). After week 52, the proportion of patients in remission did no differ between the two groups. The median time to relapse was longer for patients in the top-down group (329 d, IQR 91-not reached) compared to patients in the step-up group (174.5 d, IQR 78.5-274, P = 0.031). Results from the IBDOQs paralleled those of disease activity. At week 10, mean IBDOQ score increased by 59.2 ± 36.6 points from baseline in the top-down group and by 37.4 ± 32.8 points in the step-up group (95% CI 8.7-34.9, P = 0.0014). Patients in the top-down group received significantly less methylprednisolone than patients in the step-up group. The 95th percentile of the daily methylprednisolone dose was 35 mg for patients in the step-up group and 0 mg for those in the top-down group. On the contrary, by the end of the trial 76% of patients in the step-up group were receiving an immunomodulator agent. After the completion of the induction course of infliximab in the top-down group, the proportion of patients on infliximab was similar in both groups. There were not important differences in the occurrence of adverse events between the two groups, although the study was not primarily designed to address safety differences between the two strategies. The strongest argument for the top-down approach changing the natural history of Crohn's disease lies in the findings of the endoscopic studies performed in 49 patients of the study. At week 104, no ulcers were seen in 19/26 (73.1%) of patients in the top-down group compared with 7/23 (30.4%) in the step-up group (P = 0.0028). Endoscopic scores were 0.7 ± 1.5 and 3.1 ± 2.9, respectively (P < 0.001). This difference was marked despite the fact that there was no difference in disease activity scores between the top-down and step-up approaches at this timepoint. This leads to the notion that early introduction of biological therapy has direct benefits at an specific organ level (bowel) that far outreach the benefits of steroid sparing and overall clinical efficacy. The benefit of the early use of biological therapy has been demonstrated in rheumatoid arthritis, where the early introduction of biological therapy results in less joint damage on X-ray compared to a standard therapeutic approach using disease-modifying agents, regardless of similar clinical activity scores[10]. Mucosal healing has been associated with a reduction in hospitalizations and surgery for complications of Crohn's disease[10,21]. In the ACCENT I (A Crohn's disease Clinical study Evaluating Infliximab in a New long term Treatment regimen) trial[20], patients with short-term (week 10) and long-term (week 54) mucosal healing did no require hospitalization and patients with mucosal...
healing at only one visit required fewer hospitalizations
compared with patients without mucosal healing (18.8% vs 28%, respectively). If mucosal healing predicts a true change of natural history of the disease, these findings are of major significance.

This study has a number of aspects that should be pointed out. First, patients in the top-down group did not receive maintenance therapy with both azathioprine and infliximab. Rutgeerts et al.[21] reported a significantly higher proportion of patients with mucosal healing in a maintenance infliximab group compared with those patients who received episodic treatment (50% vs 7%; P = 0.007). Thus, the study may have underestimated the benefit of combination therapy with an immunomodulator and infliximab administered on a regular basis. Second, the data suggest that infliximab might be used as a bridge to maintenance of remission with azathioprine. In a study by Lémann et al.[23], 113 patients with steroid-dependent active Crohn’s disease were randomized to azathioprine plus placebo or infliximab 5 mg/kg at weeks 0, 2, and 6. At weeks 24 and 54, the percentage of patients in remission and off steroids was higher in the infliximab group compared to the placebo group (57% vs 29%; P = 0.003 at week 24, and 40% vs 22%; P = 0.04 at week 54). However, episodic treatment is associated with immunogenicity that leads to hypersensitivity reactions and loss of response to infliximab.[23] Third, in this study, azathioprine was started after two courses of corticosteroids, that may have underestimated the benefit of early introduction of conventional therapy with azathioprine. In a pediatric study by Markowitz et al.[24], 55 children with newly diagnosed Crohn’s disease were randomized to receive prednisone 40 mg/d with either 6-MP or placebo. Only 9% of the 6-MP treated group relapsed during a 18-mo follow-up period compared with 47% of the controls (P = 0.007). Candy et al.[26] reported similar results in 63 adult patients with active Crohn’s disease that were treated with a 12 wk diminishing dose of prednisolone and at the same time entered into a randomized, double-blind 15 mo trial of either azathioprine (2.5 mg/kg) or placebo. Remission rates between the two groups were compared at 12 wk and at 15 mo. There was no significant difference in the proportion of patients who achieved and maintained remission by week 12, but at 15 mo there was a highly significant difference in the proportion of patients in remission (42% receiving azathioprine vs 7% receiving placebo, P = 0.001). Recent practice guidelines suggest that azathioprine should be introduced with the first course of corticosteroids.[28] Fourth, this study also underscores the fact that a proportion of patients will have a good clinical outcome at 12 mo irrespective of which treatment they receive. In other words, there is a proportion of patients with newly diagnosed Crohn’s disease who do not require early intense treatment with biologic therapy.

**BILOGICS IN EARLY CROHN’S DISEASE**

Beyond achieving mucosal healing, the time of initiation of therapy might be crucial considering that a longer duration of the disease leads to more irreversible damage. There are several data in the literature that suggest higher response and remission rates to biologics in patients with a recent diagnosis of Crohn’s disease compared to those patients with long-lasting disease. In a pediatric study that included 22 children, Lionetti et al.[30] observed that the best response to infliximab was seen in children with a disease duration < 1 y. In addition, 5/6 children with early Crohn’s disease had a complete closure of all fistulas compared with 2/7 children with a disease duration of more than 1 y. Kagathan et al.[31] showed a remarkably prolonged duration of response after a single infusion of infliximab in children with early compared to late Crohn’s disease. In this study, among the 14/15 patients who responded, three of six children (50%) with early disease maintained clinical response through the 12-mo trial period, compared with none of eight children with late disease.

The CHARM (Crohn’s trial of the fully Human antibody Adalimumab for remission Maintenance) study[32] was a double-blind, placebo-controlled phase 3 trial designed to determine the efficacy and safety of adalimumab 40 mg weekly versus every other week for maintenance of clinical remission in patients with moderate-to-severe Crohn’s disease. A subanalysis of the CHARM study showed that disease duration was a significant contributor to the likelihood of achieving remission. Remission rates at weeks 26 and 54 were highest when adalimumab was started in patients within the first 2 y after Crohn’s disease diagnosis compared with patients diagnosed within > 5y (59% vs 41%, respectively at week 26; 51% vs 35%, respectively at week 54). The PRECISE 2 (The Pegylated Antibody Fragment Evaluation in Crohn’s disease: Safety and Efficacy 2) study was a randomized, double-blind, placebo-controlled trial that evaluated the efficacy of certolizumab pegol maintenance therapy in adults with moderate-to-severe Crohn’s disease.[33] In a subanalysis of the study, a high rate of response and remission was observed at week 26 in patients with Crohn’s disease diagnosed within the last 2 y and treated with certolizumab pegol compared with all patients included in the study (83.5% vs 62.8%, respectively; 61.5% vs 47.9%, respectively; P < 0.02).[30,31]

**TOP-DOWN TREATMENT: LIMITATIONS**

There is a growing evidence that suggests that the benefits of anti-TNF therapy extend beyond just the measure of clinical efficacy and that they may have the potential to alter the natural history of the disease. However, to date, several factors limit the use of biologic agents as primary therapy for Crohn’s disease patients and early intense therapy needs to be balanced against the potential risks of increased infections and malignancy. Approximately 50% of all patients with inflammatory bowel disease will never require corticosteroids. Thus, first-line therapy with biologic therapies in this group would expose patients to toxicity or immunogenicity.
without the benefit of potentially changing the natural history of their disease. The TREAT registry in North America has not shown, to date, an increased risk for malignancies or serious infections related to the use of infliximab in Crohn’s disease[32] but clinicians should be aware that opportunistic infections such as tuberculosis, hystoplasmosis or *Pneumocystis carinii* do develop in anti-TNFα-treated patients. Nevertheless, the TREAT registry also shows that in the overall population of the registry, steroid used but not infliximab treatment was an independent predictive factor for infectious complications, and this point has been confirmed in the prospective European ENCORE registry[33]. The recently reported cases of hepatosplenic T-cell lymphoma[34], a rare and aggressive tumour, which most frequently develops in young male adults treated with infliximab and concomitant immunosuppressive therapy, has raised the question of whether it is the best strategy to discontinue the immunomodulators after certain period of combined therapy, or to stop the biologic therapy and try to maintain remission with immunomodulators alone[35]. Clinicians should also balance the side effects of the new biological therapies against the well-known and frequent toxicity of both corticosteroids and immunomodulators.

**CONCLUSION**

At present, Crohn’s disease therapy is based in a sequential step-up strategy and biologic therapies are placed on a late position in this treatment strategy, mirroring the design of pivotal randomized controlled trials. However, the failure of many patients to respond to conventional therapy and the assessment that step-up strategy does not significantly alter the natural course of the disease has encouraged clinicians and investigators to question whether this late position is the most appropriate for biologics. Challenge is to identify those Crohn’s disease patients who will develop a complicated course of the disease in whom the introduction of early and more intensive treatment from the beginning of the disease can be justified. In a recent report by Beaugerie *et al*[36], young age at time of disease onset, presence of perianal disease, early need for corticosteroids, and isolated small bowel involvement were identified as clinical factors associated with poor clinical outcomes and disability. Combination of genetic and serologic profiles may have an additive value in stratifying the disease outcome[37,38] and this may help clinicians categorize patients into subgroups to better guide therapeutic decision-making.

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