Abstract
Inflammatory bowel diseases (IBD) are chronic progressive diseases. Current therapeutic strategies have not significantly altered the natural history of IBD. In the wake of other chronic diseases, such as rheumatoid arthritis, the goal of therapy has now shifted from mere control of symptoms to altering natural history to prevent bowel damage and disability. A ‘treat to target’ approach using endoscopic healing as a first definition of the target is now proposed together with tight control of inflammation based on monitoring of symptoms and biomarkers. In order to reach the target, optimization of current therapies using better understanding of pharmacokinetics is needed as well as development of predictors of disease progression to avoid under- and overtreating. Advances in the understanding of the roles of the adaptive and innate immune systems, as well as the intestinal epithelium and endothelium have resulted in the development of multiple new biologics. There is great optimism that an integrated ‘omics’ approach incorporating genetic, microbiota with clinical and environmental data will help in choosing for each patient a personalized approach targeting the mechanisms driving the disease. Finally, in this era of increasing complexity of care, education of patients to involve them in a well-informed decision-making process is mandatory.

Introduction
Inflammatory bowel diseases (IBD) are chronic disabling, progressive and destructive diseases. The goals of IBD therapy are progressively evolving from prevention of death in the 1950s to eventually prevention of the occurrence of the disease. For decades, IBD therapy was based on a so-called step-up approach where for instance in Crohn’s disease (CD) the first flare was to be treated by
steroids (such as budesonide or prednisolone), followed by azathioprine or methotrexate in cases of new flares requiring frequent steroid therapy, then monoclonal antibodies directed against tumor necrosis factor (TNF) as a final option before surgery. Current therapeutic strategies have not significantly altered the natural history of IBD. In a Danish cohort, even though mortality from ulcerative colitis (UC) decreased from 1982 to 2010, largely because of reduced mortalities from gastrointestinal disorders and colorectal cancer, people with CD had 50% greater mortality than the general population, and this value did not change over this time period [1]. In a study from Norway, 10 years after disease onset, IBD patients had an increased relative risk (RR) for disability pension as compared with the background population, the youngest patients having the highest RR [2]. The risks for surgery after diagnosis with CD and UC have decreased significantly over the past 6 decades but remain significant. In a recent systematic review based on all population-based studies, the risks for surgery 1, 5, and 10 years after diagnosis of CD were 16.3% (95% confidence interval, CI: 11.4–23.2%), 33.3% (95% CI: 26.3–42.1%), and 46.6% (95% CI: 37.7–57.7%), respectively. The risks for surgery 1, 5, and 10 years after diagnosis of UC were 4.9% (95% CI: 3.8–6.3%), 11.6% (95% CI: 9.3–14.4%), and 15.6% (95% CI: 12.5–19.6%), respectively [3]. These outcomes clearly highlight the importance of defining new therapeutic targets and strategies and the extent of unmet needs in IBD.

**New Targets in IBD**

Changes in the therapeutic paradigm of CD are resulting from its recognition as a progressive disease [4]. CD was traditionally characterized by periods of clinical remission alternating with periods of relapse defined by recurrent clinical symptoms. However, only 10% of patients experience prolonged remission of symptoms, meaning that in most cases disease activity is relapsing or continuous and, importantly, asymptomatic patients often have evidence of active inflammation on endoscopy. Persistent inflammation is believed to lead to progressive bowel damage over time, which manifests with the development of strictures, fistulae, and abscesses. These disease complications frequently lead to loss of function and need for surgical resection, which in turn lead to disability (fig. 1). As in other chronic destructive diseases such as rheumatoid arthritis, treatment paradigm is currently shifting in CD from mere control of symptoms towards the improvement of long-term disease outcomes, i.e. reduced structural damage and disability [5, 6]. A new instrument, the Leman score, has thus been developed to measure the cumulative structural bowel damage caused by CD over
time and to assess the impact of new treatment strategies on long-term outcomes [6].

The introduction of novel therapies and the development of new approaches to treatment in several chronic diseases such as rheumatoid arthritis led to better outcomes for patients. Prominent among these is a ‘treat to target’ strategy that is based on regular assessment of disease activity using objective outcome measures and the subsequent adjustment of treatments. This approach is currently explored in CD. However, there is currently no accepted, well-defined, comprehensive treatment goal that entails the treatment of both clinical symptoms and biologic inflammation. As a starting point, a working definition of sustained deep remission (that includes long-term biological remission and symptom control) with defined patient outcomes (including no disease progression) has been proposed [7–9]. The concept of sustained deep remission represents a goal for CD management that may still evolve. Clinical trials are needed to evaluate whether treatment algorithms that tailor therapy to achieve deep remission in patients with CD can prevent disease progression and disability.

Assessment of objective measures of inflammation is an increasingly important part of the management of IBD. Thorough assessment of disease activity and extent at presentation is needed to ensure a correct diagnosis of IBD (vs.
non-IBD) and of CD (vs. UC), avoid delay in diagnosis, identify complications, help assess prognosis and take appropriate therapeutic decision. During follow-up, clinical decision-making is increasingly being driven by the findings of continued monitoring (for objective evidence of inflammation), with the aim of optimizing treatment for tight disease control. Despite the potential benefits of longitudinal monitoring in CD, there are several unanswered questions around implementing this model in practice: Which monitoring tools should be used? When should they be used? How should the monitoring strategy differ in different patient scenarios? Given the uncertainties around these issues, practice recommendations were recently developed based on the best published evidence available and/or expert opinion [10]. A number of ongoing clinical studies will provide further data and assess the impact on clinical outcomes of a ‘tight control’ approach to treatment based around objective parameters of inflammation beyond mere control of symptoms.

Complementary to the treat to target concept is early intervention: losing time in high-risk patients will lead to less chance to reach the target and increased risk of further progression and bowel damage. In this regard, targeting CD early might be the only way to change the disease course [11, 12]. In 2012, an international definition of early CD was proposed and defined by disease duration ≤ 18 months and no previous use of disease-modifying agents [13]. However, early introduction of disease-modifying anti-IBD drugs cannot be recommended in all patients with CD. First, scientific evidence from prospective studies is still lacking. An open-label RCT comparing early combined immunosuppression [three infusions of infliximab (5 mg/kg body weight) at weeks 0, 2 and 6 with azathioprine, and, if necessary, corticosteroids] or conventional treatment (corticosteroids, followed, in sequence, by azathioprine and infliximab) in CD of <4 years’ duration showed a higher remission rate within the first year in the top-down group than in the control groups, but this difference disappeared at week 78 [14]. More recently, the RAPID (Effect of Early Prescription of Immunosuppressants on First Three-Year Course of Crohn’s Disease) study from the Groupe d’Etudes des Thérapeutiques et Affections inflammatoires Digestives (GETAID) compared two therapeutic approaches in patients with CD who had an established diagnosis of the disease for <6 months. The patients were treated either with early use of immunosuppressants or with a step-up approach. No difference was observed between the two groups regarding the number of trimesters without disease activity, with steroids, infliximab, surgery, or requirement for hospitalization [15]. Second, it is necessary to identify patients with CD who are at a high risk of having a complicated and/or severe disease course and who could benefit from a more aggressive therapeutic strategy in order to avoid overtreatment.
Optimization

Although new biologics are highly effective for induction and maintenance of clinical remission, not all patients respond, and a high proportion of patients lose response over time. There is thus a strong need for optimization. Little is known about their exposure-response relationship and the factors that may affect their disposition. Understanding these factors is essential to further improving the therapeutic efficacy of these drugs [12]. Monitoring serum drug concentrations and antibodies (immunogenicity) may lead to more appropriate therapeutic management in patients with loss of response. The pharmacokinetics of biologics appears to be strongly influenced by several factors related to patient and disease characteristics such as age, BMI, albumin level, CRP and combination therapy with immunomodulators. Evaluation of the covariates that influence drug disposition may help to carefully select those patients that are more likely to benefit from receiving higher doses due to an accelerated clearance. Several descriptive studies and post hoc analyses from clinical trials have reported consistent associations between serum anti-TNFs and antibody levels and clinical responses. Algorithms have been proposed in which interventions are based on a combined assessment of IFX bioavailability and immunogenicity at the time of therapeutic failure [16]. The first prospective study showing the cost-effectiveness of interventions defined by this kind of algorithm has recently been published [17]. The number of approved biologics for the treatment of IBD is expected to increase in the forthcoming years. Therefore, a better understanding of the factors that impact the pharmacokinetics and pharmacodynamics of biologics is crucial to ensure more efficient dosing regimens which in turn may enhance the therapeutic success of these therapies.

Prediction

At present, three possible treatment strategies could be considered in CD: (1) classical step care; (2) immunosuppressives in combination with a tapering course of steroids (accelerated step care), and (3) TNF antagonists (either as monotherapy or in combination with immunosuppressants) [11]. An essential prerequisite of any treatment paradigm is recognition that overtreatment of low-risk patients will result in a poor therapeutic index. Consequently, it is essential to identify patients who are suitable for early treatment because they are
at high risk of disease progression. Several clinical markers (disease location, extent and behavior, age, mucosal aspect, tobacco used), and possibly serologic and genetic markers have been considered as predictors of disease outcome [reviewed in 11]. However, few of these markers have been tested prospectively, and the definition of disease ‘outcome’ has been inconsistent throughout these studies. Still, algorithms based on existing knowledge have been proposed [11]. Prospective trials to evaluate (a) the relevance of markers to predict long-term outcomes such as bowel damage and disability and (b) the benefit of early intervention in patients with CD who are at high risk of disease progression are urgently needed.

**Personalization**

Advances in the understanding of the roles of the adaptive and innate immune systems as well as the intestinal epithelium and endothelium have resulted in the development of multiple biologics that all represent an alternative to the use of current therapies in patients with refractory CD or UC. However, there is a huge potential for variation in inflammatory response from patient to patient and within a single patient over time and then in response to different treatments. Even when all classical aspects of a disease phenotype are present, the mechanism responsible for the pathology observed may differ from one person to another. Genome-wide association studies have revealed a wealth of genes potentially involved in CD and UC, but no single gene or set of genes is prognostic. A new view of the genotype-phenotype relationship in which different sets of loci are responsible for mechanistically distinct subtypes of diseases has been proposed [18]. It is possible that the future of IBD therapy would include computing gene and protein function for a more targeted, personalized patient-based approach.

**Education**

Disease-related knowledge is associated with quality of life, coping skills and medication adherence. Several surveys have shown that IBD patients are ill-informed about their disease and its associated risks. Improvement of patient education is necessary to appropriately involve patients in the decision-making process. There are limitations in education linked to poor access to specialized centers. Studies from Scandinavia have shown that these limitations may be overcome by personalized self-management training of patients. A web-guided
approach was shown to be feasible, safe and cost effective [19]. It empowers patients with UC without increasing their morbidity and depression. Such initiatives should be further tested.

**Conclusion**

The treatment of IBD is rapidly evolving. Together with the development of new drugs, new therapeutic goals and new strategies have emerged in order to alter the progressive natural course of IBD. As in other chronic diseases, a treat to target approach with ‘tight control’ based on monitoring is now proposed. However, it must be recognized that these concepts have not been validated, and prospective studies to evaluate their long-term impact on new end points such as bowel damage and patients’ functional status are needed.

**Disclosure Statement**

J.-F. Colombel has served as consultant, advisory board member or speaker for Abbvie, Amgen, Bristol Meyers Squibb, Celltrion, Ferring, Genentech, Giuliani SPA, Given Imaging, Merck & Co., Millennium Pharmaceuticals Inc., Nutrition Science Partners Ltd., Pfizer Inc., Prometheus Laboratories, Sanofi, Schering Plough Corporation, Takeda, Teva Pharmaceuticals, UCB Pharma, Vertex, Dr. August Wolff GmbH & Co.

**References**